**NEAR EAST UNIVERSITY**
**INSTITUTE OF GRADUATE STUDIES**
**DEPARTMENT OF PHARMACEUTICAL TECHNOLOGY**

# USING COMPACTION SIMULATOR AND DESIGN OF EXPERIMENT (DoE) APPROACH; CHARACTERIZATION AND EVALUATION OF DIRECT COMPRESSED PARACETAMOL POWDER

**POSTGRADUATE THESIS**

**Musaab SAADA**

**NICOSIA**
**June, 2021**

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**Nicosia**
**June, 2021**

## Approval

We certify that we have read the thesis submitted by Musaab SAADA titled **"Using Compaction Simulator and Design of Experiment (DoE) Approach; Characterization and Evaluation of Direct Compressed Paracetamol Powder"** and that in our combined opinion, it is fully adequate, in scope and quality, as a thesis for the degree of Ph.D. in Pharmaceutical Technology.

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## Declaration

Hereby I declare that this thesis study is my own study. I had no unethical behaviour in all stages from the planning of the thesis until writing thereof. I obtained all the information in this thesis in academic and ethical rules. I provided reference to all of the information and comments which could not be obtained by this thesis study and took these references into the reference list, and had no behaviour of breaching patent rights and copyright infringement during the study and writing of this thesis.

Musaab SAADA
19/08/2021

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## Abstract

# USING COMPACTION SIMULATOR AND DESIGN OF EXPERIMENT (DoE) APPROACH; CHARACTERIZATION AND EVALUATION OF DIRECT COMPRESSED PARACETAMOL POWDER

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**Aim:** This study aims to combine the compaction simulator and QbD approach along with DoE to investigate the compaction behaviour and evaluate the final product quality for two types of Directly Compressible Paracetamol powder to achieve the optimum final product.

**Material and Method:** Two different types (A and B) of DC Paracetamol powder with three consecutive batches were investigated using the Compaction simulator and QbD approach. In this study, differences in DC Paracetamol granulation process and the sieve (mesh) size was evaluated. Powder characteristics for three consecutive batches of each type were assessed. Applied forces with Compaction Simulator were selected as 15, 30, 45 kN. Tablet results were evaluated considering batch to batch powder differences, compaction behaviours and energy utilization. Single round 11,28 mm punch, three applied forces with constant speed (10 rpm) was selected for tabletting process with Stylcam R200.

Different force effect on pressed tablets was measured. Statistically one-way ANOVA test was used for calculations to identify batch to batch variation in compaction behaviour.

QbD approach was enrolled, and its steps were followed, starting from defining the QTPP, continuing with defining the CPPs, then CQAs after risk assessment study, and ending with forming a design space study by using the DoE program (MODDE 12.1).

**Findings and Results:** It was found that DC paracetamol Type B had better compaction behaviour than Type A and required less energy during compression. Additionally, better flowability and compressibility were observed in Type B.

The results of QbD investigation showed that Type B Paracetamol powder was compressed at 16.4 kN compaction force, that will result in tablets that reach the maximum quality of the final product with desirable characteristics based on QTPP standards for Paracetamol tablet without adding any excipient.



***Key Words**:* DC paracetamol powder, compaction simulator, quality by design.

## Özet

# SIKIŞTIRMA SİMÜLATÖRÜ VE DENEY TASARIM YAKLAŞIMI (DoE) KULLANILARAK, DİREK BASKIYA UYGUN PARASETAMOL TOZUNUN KARAKTERİZASYONU VE DEĞERLENDİRMESİ

**SAADA, Musaab**

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**Haziran, 2021, (166) sayfa**

**Amaç:** Bu çalışma, sıkıştırma simülatörü ile deney tasarımı metodu ile kalite tasarımı (QbD) yaklaşımını (QbD) birleştirerek; optimum nihai ürünü elde etmek için direk baskıya (DC) uygun iki farklı tipte Parasetamol tozun sıkışabilme davranışını araştırmayı ve nihai ürün kalitesini değerlendirmeyi amaçlamaktadır.

**Materyal ve Metod:** İki farklı tipte (A ve B) ve herbirinden üç ardışık seri direk baskıya uygun Parasetamol toz kalite tasarımı yaklaşımı kullanılarak sıkıştırma simülatördeki çalışmalarla incelenmiştir. Bu çalışmada granülasyon prosesiyle DC özellik kazandırılmış parasetamol elek boyutu (mesh) etkisi değerlendirilmiştir. Her iki tip toz için üç ardaşık serinin karakterizasyonu değerlendirilmiştir. Sıkıştırma simülatöründe 15, 30, 45 kN'luk baskı kuvvetleri kullanılmıştır. Tablet sonuçları, seriden seriye toz farklılıkları, sıkıştırma davranışları ve enerji kullanımı dikkate alınarak değerlendirilmiştir. Tablet baskı işlemi Stylcam R200 ile, tekli yuvarlak 11.28 mm'lik zımba kullanılarak, 3 farklı baskı kuvvetiyle ve sabit hızda (10rpm) tamamlanmıştır. Farklı kuvvet uygulamalarının basılmış tabletler üzerindeki etkisi ölçülmüştür. Sıkıştırma davranışında partiden partiye oluşan farklılıkların belirlenebilmesi için İstatistiksel tek yönlü ANOVA testi gerekli hesaplamalarda kullanılmıştır. Kalite tasarımı yaklaşımı kayıt altına alınmış ve kalite hedef ürün profili (QTPP) 'nin tanımlanmasından başlayarak adımları takip edilmiştir,Kritik proses parametrelerinin (CPP') tanımlanmasıyla çalışmalara devam edilmiş, ardından risk değerlendirme çalışmasından sonra kritik kalite özellikleri (CQA) ve deney tasarım programı (MODDE 12.1) kullanılarak tasarım alanı çalışması oluşturmuştur.

**Bulgular ve Sonuçlar:** Tip B' nin Direk baskı parasetamol tozun Tip A'dan daha iyi sıkışabilme özelliğine sahip olduğu ve sıkıştırma sırasında daha az enerji gerektirdiği tespit edilmiştir. Ayrıca ek olarak akışkanlık ve basılabilmesinin de Tip B daha iyi olduğu gözlemlenmiştir. QbD çalışmasının sonuçları; Tip B Parasetamol tozunun 16.4 kN sıkıştırma kuvveti ile nihai ürünün maksimum kalitesine

ulaşan tabletlerin hazırlandığı ve Parasetamol tablet için QTPP standartlarına dayalı olarak istenen özelliklerin herhangi bir yardımcı madde eklemeden elde edildiğini göstermiştir.

**Anahtar Kelimeler:** Parasetamol Direk Baskı tozu, sıkıştırma simülatörü, kalite tasarımı

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## List of Abbreviations

| | |
|---|---|
| **ANDA**: | Abbreviated New Drug Application |
| **ANOVA**: | Analysis of variance |
| **API:** | Active Pharmaceutical Ingredient |
| **API:** | Pharmaceutical Ingredient |
| **BCS:** | Biopharmaceutical Classification System |
| **BET**: | Brunauer–Emmett–Teller |
| **cGMP**: | Current Good Manufacturing Practice |
| **°C:** | Degrees Celsius |
| **$cm^3$:** | Cubic Centimetre |
| **CMA:** | Critical Material Attributes |
| **CMC:** | Critical Micelle Concentration |
| **CPP:** | Critical Process Parameters |
| **CQA:** | Critical Quality Attributes |
| **D:** | The Relative Density |
| **DC:** | Direct Compression |
| **DEM**: | Discrete Element Method |
| **DoE:** | Design of Experiments |
| **DS**: | Drug Substance |
| **DSE**: | Design Space Estimation |
| **E**: | Porosity |
| **EP:** | European pharmacopoeia |
| **FDA:** | Food and Drug Administration |
| **FEM**: | The Finite Element Method |
| **FMEA:** | Failure mode effects analysis |
| **g:** | Gram |
| **ICH:** | International Conference on Harmonization |
| **ISO**: | International organization for standardization |
| **K:** | Slope |
| **kN:** | Kilonewton |

| | |
|---|---|
| **kg:** | Kilogram |
| **L:** | Litre |
| **m:** | Meter |
| **MCC:** | Microcrystalline cellulose |
| **mg:** | Milligram |
| **min.**: | Minute |
| **ml:** | Millilitre |
| **mm:** | Millimetre |
| **N:** | Newton |
| **NDA**: | New Drug Application |
| **P:** | The Pressure |
| **PAT:** | Process Analytical Technology |
| **PLS**: | partial least squares |
| **Py:** | Yield Pressure |
| **QbD:** | Quality by Design |
| **QTPP:** | Quality Target Product Profile |
| **$R^2$:** | The Coefficient of Determination |
| **RLD**: | Reference Listed Drug |
| **rpm:** | Revolutions per Minute |
| **SD:** | standard deviation |
| **SEM:** | Scanning Electron Microscope |
| **TPP:** | Target Product Profile |
| **USP:** | The United States Pharmacopeia |
| **W/W:** | Weight Concentration |
| **θ:** | Theta |
| **µm:** | Micrometre |

# CHAPTER I
## Introduction

Paracetamol (acetaminophen) is a long-invented, antipyretic analgesic, which is the most broadly prescribed and used drug worldwide. It is an analgesic that is used to ease the pain and fever in both adults and children (Prescott, 2000). Although the production of high-quality paracetamol tablets gained tremendous significance because of their extensive usage, Paracetamol powders have the characteristic of a poorly compressible material which is the reason for adding the excipients that improve the compressibility of the powder (Hong-guang & Ru-hua, 1995). This is one of the reasons why many powder manufacturing companies are competing to produce the best DC paracetamol powder and finding the best way to process and prepare its formulation to yield high-quality paracetamol tablets. One of the paracetamol powder production mechanisms is wet granulation processing. Wet granulation is a tablet manufacturing technique where particle size enlargement takes place (Iveson, et al., 2001). There are a variety of advantages that come along with wet granulation processing, such as increase the compressibility of the powder, improve the flowability, and lower the amount of dust during manufacturing, transferring, and storage processes (Ofoefule, 2002). Compaction tests are necessary in order to secure a low level of variation with the desired product as a result. However, small changes in powder characteristics lead to multiple variable compaction test results (Zhang & & Mao, 2017).

A compaction simulator should be used, a machine designed specifically for simulating and mimicking the precise tabletting cycle process andapable of recording all the significant parameters during the compaction process (Çelik & Marshall, 1989). Compression is well-defined as a decrease in the bulk volume of materials due to the displacement of the gassy phase (Marshall, 1986). The mechanisms during the compaction of pharmaceuticals are essential in the design and improvement of solid dosage forms. Those mechanisms are as follows: Preliminary particle rearrangement, fragmentation and elastic, plastic, and viscoelastic deformation of the particles, which significantly affect the derived compaction behaviour (Roberts & Rowe, 1987; Bogda, 2002). Powder properties highly affect the compaction behaviour, such as the surface area of powder particles,

which is contrarily related to a particle size that widely affects compaction behaviour and tablets characteristics such as particle rearrangement, plastic, elastic energies (Tay, et al., 2019), control tests (hardness, friability, and disintegration (Koynov, et al., 2013; Eiliazadeh, et al., 2004). Furthermore, particles with higher compressibility are generally smaller in size and more cohesive as a consequence of inter-particle cohesive forces compared to the weight of the particles (McKenna & McCafferty, 1982). The mechanical strength of the tablet is also strengthened by small particles, If increase smaller particle, the higher the mechanical strength of the tablet we increase (De Boer, et al., 2004).

Heckel plot is one of the most popular models used in correlation studies (Heckel, 1961). One of the correlations that have been studied using Heckels' equation is the effects of plastic and brittle behaviour (Geoffroy & Carstensen, 1991). The mean yield pressure (*Py*) given by Heckels' plot is inversely related to plastic deformation and densification. This means that when the *Py* value is low, deformation and densification are high and vice versa (Osamura, et al., 2016).

Several tests should be applied for quality assurance of the product. In the pharmaceutical industry in the past, it was known to assess the quality after the final product was produced, which was a time-consuming method. Furthermore, in case of failure of the test, the whole batch was disposed, and the manufacturing of a new product was started from the beginning (Zhang & & Mao, 2017). In these recent years and after the development of human knowledge in several aspects of science. A variety of sciences were crossing ways at several points where these sciences can support and improve each other in beneficial ways. On the path of pharmaceutical industry development, other sciences such as mathematical sciences and electronic and technical technology along with pharmaceutical technology crossed over and gathered to provide less time consuming, cost-saving, and higher quality assurance methods of producing a specific drug product. The method produced by the combination of these sciences is quality by design (QbD) which allows assuring the quality of a product before the actual production by using technological instruments to apply the factors that affect the quality of the final product and mathematical statistics to increase the reliability of the results (Somma, 2007; Aksu & Mesut, 2015). Quality by design (QbD) is defined "as a systematic, risk-based, and scientific approach to pharmaceutical industry development that begins with

predetermined goals, it gives prominence to the product, process understanding and process control based on risk assessment techniques" (García-Valcárcel, 2008). It also entails an advanced scientific understanding of critical process and final product characteristics, as well as the design of controls and tests based on scientific boundaries of understanding defined during the development phase, as well as the use of previous production knowledge to improve quality (Lawrence, 2008).

The employment of QbD in the pharmaceutical district has been described and illustrated in the ICH (International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use) Q8 (pharmaceutical development), ICH Q9 (quality risk management), ICH Q10 (Pharmaceutical quality system), and ICH Q11 (development and manufacture of drug substances). These are excellent instructions for the scope and definition of QbD, as well as the prerequisites for its application in the biopharmaceutical industry (Lawrence, et al., 2014).

The concept of QbD consists of several steps that should be fulfilled and appropriately completed. The initial step is to define a quality target product profile (QTPP) according to prior scientific knowledge. Secondly, identification of critical quality attributes CQAs and critical process parameters CPPs. Thirdly, studying risks on the product's quality. Fourthly, the Establishment of multivariate experiments by consuming Design of Experiments (DoE) to identify the relationships between CQAs and CPPs and develop a design space. Finally, controlling the industrial process and operating within the yielded design space for the product quality assurance (Kan, et al., 2014). During the DoE study, the MODDE program has been used in order to establish a design space study based on knowledge space.

This thesis was done to investigate differences and quality of 2 Types and three consecutive batches of paracetamol DC (Atabay, Turkey) using compaction simulator.

The compaction simulator was used to apply different compaction forces (15, 30, and 45kN) to determine each type's compaction behaviour and their differences. The compaction simulator program relies on force–displacement curve to assess energy utilization during the compression process.

The QbD approach was employed to find the optimal CPPs to generate the best, and the most quality assured final drug product, which can be compressed without the addition of any type of excipients.

**Statement of Problem**

The problem is the poor compressibility of pure paracetamol powder that leads to requirements for excipients and/or granulation process utilization and affects the final product quality, which is considered to be time-consuming, financially expensive, and low quality of the final product.

With the wide range spread of DC Paracetamol products in the markets worldwide, it is of high importance to evaluate those products and pick a DC Paracetamol formulation that complies the best with the manufacturer's economic standards compared to any other DC Paracetamol formulation.

**Purpose of The Study**

1- Batch to batch variation of final powder product characterization by quality parameters with compaction simulator.
2- Employing the QbD approach in developing and producing a higher quality of Paracetamol compacted powder in less time and with fewer requirements.
3- By employing the compaction simulator and QbD approach, we aim to find the best paracetamol type of the two types.

**Research questions/hypotheses**

1- Does the employment of the compaction simulator help in determining the compaction behaviour of each type?
2- How do the powder properties (surface area of the particles, particle size, flowability, etc.) of each type affect its compaction behaviour?
3- What are the CPPs picked in the development of the Paracetamol compacted powder, and how we optimize them?
4- How could we link the CQAs to the CPPs in order to create a design space study?

5- Was it possible to form a Compacted Paracetamol powder (tablets) without the need for excipient addition after the QbD approach enrolment in the study?

**Significance of the study**

Evaluation of Paracetamol powder offered previously in the market and investigating the possibility of compacting the powder without any excipient addition, fewer requirements, and higher quality using compaction simulator, QbD approach, and DoE program.

**Limitations**

1- Insufficient accessibility for all the required tools, instruments and programs to expand the study.
2- The knowledge of the exact type of the excipient added to the Paracetamol powder.
3- Time constrictions prevented our progress from completing other investigations that could be done in the research.

**Definition of Terms**

**Paracetamol:** also called acetaminophen, is a drug that belongs to a class of drugs called 'antipyretics' which are used for lowering the body temperature (fever) and have analgesic effects.

**Pharmaceutical Excipient:** a substance that is added to a particular active ingredient for a drug to improve the therapeutic effects (such as drug absorption, solubility, and viscosity) and also to improve the manufacturing process by improving powder compressibility and flowability.

**Compaction Simulator:** a machine that is used for mimicking the exact tabletting cycle process.

**Compression:** a reduction in the bulk volume of materials.

**Compressibility:** the ability of a pharmaceutical powder to undergo a volume reduction when pressure is applied.

**Flowability:** the capability of a powder to flow in a unidirectional way under specific circumstances.

**Quality by Design:** a systematic, risk-based, and scientific approach to pharmaceutical industry development that begins with predetermined goals and gives prominence to the product, process understanding and process control based on risk assessment techniques.

**Quality Target Product Profile:** a prospective summary of the quality characteristics of a drug product that ideally will be achieved to ensure the desired quality, taking into account the safety and efficacy of the drug product.

**Critical Material Attributes:** physical, chemical, biological or microbiological properties, features, or characteristics of an input material that must be within an appropriate limit, range, or distribution to ensure the desired drug substance, in-process material, or excipient quality.

**Critical Process Parameters:** Input operating parameters or process state variables of a unit operation or process step.

**Critical Quality Attributes:** physical, chemical, biological or microbiological properties, features, or characteristics of an output material involving accomplished drug

product that must be within an appropriate limit, range, or distribution to ensure the desired product quality.

**Design of Experiment:** highly systematic branch of QbD that illustrates the relationship between the independent variables CPPs and the dependent variables CQAs to reach the optimal process characteristics and drug product quality.

**Design Space:** the multidimensional combination and interaction of input variables and process parameters that have been demonstrated to provide assurance of quality.

# CHAPTER II

# Literature Review

## Theoretical Framework

### *Oral route*

The oral (enteral) route is one of the best favourable routes among all the pharmaceutical drug administration routes where the transportation of the drugs and chemical agents to the systemic circulation through the digestive system occurs (Kipping & Rein, 2012).

Usually, it is the first route used in the treatment of any disease (except urgent, emergent, and special cases) because of its safety, feasibility, convenience, and most economical. Different dosage forms are administrated orally, such as emulsions, suspensions, solutions, gels, powders, capsules, and tablets being the most frequently used dosage form of all these oral dosage forms.

Tablets are chemically and physically stable, provide an accurate and reproducible dose, can optimize drug effects, relatively easy to produce, and less cost consuming in manufacturing. Another advantage of oral route consumption is the prolonged effect of a drug, while the disadvantages are the delayed time of the occurrence of an effect of a drug, odour or taste, nausea, vomiting, and gastric mucosal irritation (Aguirre, et al., 2016).

### *Paracetamol*

Paracetamol (acetaminophen) is an antipyretic compound, which is commonly used because of its analgesic effects on pain and the ability to improve the symptoms of fever safely compared to non-steroidal anti-inflammatory drugs (Brune & Zeilhofer, 2003). The safety of its usage made it widely spread in both adults and children until it became the most popular analgesic drug sold and used worldwide. It was firstly synthesized by Morse in 1878 and used for the first time in a clinical case in 1887 by Von Merring (Morse, 1878; Von Mering, 1893). The concerns about its safety delayed its spread until 1970. After almost a century of paracetamol synthesis, it became the top best-selling pharmaceutical analgesic in so many countries until now (Von Mering, 1893).

**Solubility**

Paracetamol [N-(4-hydroxyphenyl) acetamide] is a solid white crystalline powder with a slight solubility in water (one part is soluble in seventy parts of water at room temperature); however, it is very soluble in hot water and shows free solubility in Alcohol (Merck, 2006). It's naturally a weakly acidic compound based on its pKa, which equals 9.5 at 25'C with a melting point of 168-172'C and shows a maximal UV absorption at a wavelength of 249nm (Sweetman, 2009).

**Biopharmaceutics Classification System (BCS)**

Drugs are classified into four broad categories based on their solubility and permeability, according to the BCS.

Class I: highly soluble and highly permeable

Class II: poorly soluble but highly permeable

Class III: highly soluble but poorly permeable

Class IV: poorly soluble and poorly permeable

Paracetamol was previously categorized as a BCS class III compound, but after a technical report by the WHO expert committee on pharmaceutical preparation requirements, it is now classed as a BCS class I molecule. The term "highly permeable" refers to an API that is absorbed at a rate of at least 85%. In the WHO multisource publication, the permeability requirement was lowered from 90% in the FDA guidance to 85%. Paracetamol is an example of an API that was previously classified as Class III and is now included in BCS Class I (Kalantzi, et al., 2006).

**Powder Characterization**

The zig-zag form of the crystal lattice structure of paracetamol powder is known to have poor compression. This crystal structure produces a lot of elastic deformation, which affects mechanical strength and capping. In the crystal lattice, the creation of planar structures causes the metastable polymorphic form of paracetamol to plastically recover deform and exhibit a reduced elastic recovery. For all of this reasons that result in non-optimal outcomes when tabletting because of the occurrence of different obstacles such

as capped, laminated, and brittle tablets yielded. Compression characteristics of powders are mainly affected by their physical properties (Hong-guang & Ru-hua, 1995).

For this reason, excipients are usually used in combination with Paracetamol powder to improve the outcome of the tabletting process ending up with a well-compressible formulation with satisfying pharmacokinetic and pharmacodynamics properties, which is considered to be the challenging point for most of the pharmaceutical companies in the Paracetamol industry. The development of a new Paracetamol formulation (DC Paracetamol powder) became the goal of many pharmaceutical industrial companies that aim to create the optimal mixture of drug-excipients combination, comprehensive knowledge of the physical, chemical, and mechanical characteristics of the formulation components is required to produce the optimum final product tablet with the highest drug bioavailability, therapeutic efficacy, and safety profile.

***Pharmaceutical Powder***

A pharmaceutical powder is a chemical or combination of finely split medications with or without excipients that is solid in a physical form and intended for internal (oral powders) or external (topical or dusting powder) usage. It is made up of many different particles ranging in size from 1m to 1000m. This powder could be gained by comminution and crushing. Mostly, powders are more vulnerable to be solubilized, which leads to rapid absorption of the active ingredient carried by the powder (Dash, et al., 2013).

The volume involved by a powder framework is ordinarily more prominent than the consolidated volume of the separate particles. As an outcome of the irregular pressing of the discrete particles, the leftover volume is made out of voids. These voids are occupied by air. The incidence of the voids (pores) considers the particles to transfer comparatively with one another, which is the principal movement for powder flow. The making particles out of a powder framework can be either primary or secondary particles (Dash, et al., 2013).

Primary particles are specific entities, as their name suggests, whereas secondary particles are agglomerates or granules made up of two or more primary particles. Granulation or cohesive/adhesive forces between main particles in a powder bed can be used to accomplish this (Staniforth & Aulton, 2007).

Where granulation is included, the secondary particles can appear as unpredictable coarse agglomerates or round agglomerates (pellets) (Johansson & Alderborn, 2001). These secondary particles are permeable, when it comes to powder compression, their interior porosity becomes a variable in the overall reaction of the powder to compression pressure, which adds another degree of complexity. (Wikberg & Alderborn, 1991; Berggren & Alderborn, 2001).

## Particle Size and Shape

### *Importance of particle size and shape in pharmaceutical manufacturing*

Powder behaviour is influenced by particle size in a variety of ways. The relative sizes of the components influence the ability to generate uniform mixes when mixing materials together. As a result, it's usually preferable if the component materials' sizes are similar. Mixing performance is influenced by particle size and inter-particular adhesion.

Flow and packing affects Powder properties with small particle sizes have higher friction and adhesion forces between particles, resulting in decreased flowability and increased flow as particle size increases. The impact of surface area and particle size on granulation times and the amount of liquid required.

The particle size and particle size distribution have an impact on the packing density of powders.

The powder's capacity to densify under pressure influences its tabletting characteristics. As a result, the tabletting process is influenced by both packing density and particle size. Granulation can change the character of particle surfaces by promoting contamination and hence altering inter-particular adhesion strength.

Surface area influences the rate of dissolution and bioavailability of materials. Small-particle powders have a higher specific surface area than larger-particle powders. Controlling particle size is especially important for formulators working with poorly soluble substances. Components added to liquid formulations may have substantial dissolution times.

### *Particle size analysis*

Data on particle size may be acquired using a variety of ways. Cumulative, differential, and histogram data are the three types of data available. A histogram plot

depicts the fraction inside a certain size interval. A cumulative graph depicts the proportion of particles having a size less than a particular value. This plot is often sigmoid in shape. The first derivative of a cumulative plot is called a differential plot. The differential and histogram charts may appear to be the same, but they are not. When data is provided, the type of plot used should be specified. The following is a list of the most frequent instrument types used in the pharmaceutical industry.

- Optical and Scanning Electron Microscopy.
- Laser Diffraction -Mie and Fraunhoffer Diffraction.
- Sieves.
- Light Obscuration (HIAC and PSS Accusizer).

### *Tablet Technology*

#### Tablet

Tablets are the most popular dose form in both administration and industrial aspects. Their formulation comprises of many components with a range of functions and characteristics. In most instances, tablets are composed of Active Pharmaceutical Ingredient (API) with or without pharmacologically inert excipients such binders, anti-adherents, diluents, carriers, etc. Depending on the compressibility of the API powder (Wen, et al., 2015).

The powder material may be granulated to enhance manufacturability, or it could be compressed directly into tablets. The physical and chemical quality of the raw material is characterized in the pre-formulation phase according to pharmacopoeia-specified tests. During the production process, samples are gathered and analysed. When the final product is achieved, an end-point check ensures its quality. (Kottke & Rudnic, 2002).

Tensile strength and crushing strength of the finished tablet may be used to characterize the mechanical strength of the tablets. During the production process, tablets must retain their physical, chemical, and dosage consistency. The tablet should be able to resist attrition during packing, transportation, and storage while also being easily split by hand. The dissolving profile is influenced by the tablet strength, which influences how quickly or slowly the medication takes action. Some tablets should be chewed, while others should be dissolved or dispersed in water before consumption, and yet others should

be kept in the mouth to allow the active ingredient to be released (Narang, et al., 2010; Prajapati, et al., 2009).

Because of the diversity of consumption modalities, consistency, and manufacturing methods, tablets have many characteristics and many detailed categories. Tablets are typically solid, with flat or convex end surfaces and bevelled edges, allowing for a variety of circular, triangular, rectangular, and other forms. Also, break lines could be present along with a symbol or another marking. Suitable measures are taken during manufacturing, packaging, storage and distribution of tablets to maintain their microbial quality (Podczeck, 2012; Pitt & Heasley, 2013).

**Tabletting**

Pharmaceutical tablet production includes compression of free-flowing powder in an encircled cylindrical cavity of defined geometry (die cavity), located within a die, which is itself positioned in a die table (Summers & Aulton, 2007), in other words, The term "tabletting" refers to a decrease in the bulk volume of powder as a result of the gaseous phase shifting. The stages involved in powdered solids bulk reduction.

***Tabletting process.*** Initial repacking of particles starts once the powder is placed and packed into the die cavity even before the upper punch starts to descend and enter the die cavity, the forces that affect the powder particles consist of those which are related to the packing properties, density, and the total mass of the particles which are located in the die cavity.

When the upper punch starts to compress the powder particles in the die in a uniaxial direction, volume reduction starts to occur progressively through rearranging the powder particles and decreasing the distance between them by outer mechanical force applied. This process is the main mechanism of the initial repacking of the particles (Marshall, 1986; Bogda, 2002).

After further compression of the powder particles, it will reach a limit where it can’t be rearranged more, and a reversible deformation which is called elastic deformation that causes the particles to be deformed under a certain amount of compression and get

back to normal as soon as the compressive force is removed, starts to take place (Marshall, 1986; Bogda, 2002).

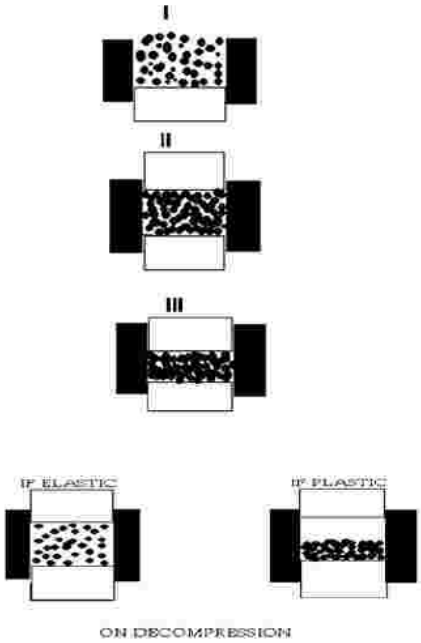
When the compression is reached to the elastic limit, which means that there is no ability for more elastic deformation, an irreversible deformation that causes a permanent alteration in the shapes of particles, this alteration leads to a preservation of the inter-particulate bonds referred to as plastic energy.

When elastic and plastic deformations reach their maximum and further compression is applied, particles tend to be fragmented and broke until all the voids and spaces between the particles are filled and eliminated. After plastic deformation and or fragmentation, removal of the mechanical force and decompression begins (Çelik, 1996; Odeku, 2007).

The stress relaxation process immediately begins, and the elastic deformation will fade away, and the particles will recover. The stress relaxation process may continue even after a full removal of the punch and may include a plastic flow (Odeku, 2007).

Figure 1

*Stages involved in compression (I-III) and decompression (Odeku, 2007)*




The decompression stage follows the compression stage in the tabletting cycle, in which the applied load is removed. The decompression stage is not less important than the

compression stage because it is an effective factor in determining whether satisfactory tablets will form after tablet formulation or not. Several deformation mechanisms, for example, are time-dependent and may be active at different rates throughout the tabletting cycle, ensuring that the tablet is never at a stress/strain equilibrium during the tabletting process.

This demonstrates that when time dependency is considerable, the criticality of the rate at which a load is delivered or withdrawn may be high. A brittle fracture of a plastically deforming solid may occur if the loading (or unloading) of the solid is done too quickly. As a result, as current study studies have shown, tablet formulations' capping and lamination tendencies are linked and related to their plastic and elastic behaviour throughout the tabletting cycle (compression, decompression, and ejection) (Carless & Leigh, 1974; Itiola & Pilpel, 1986).

During compression and decompression stages, the same deformations characteristics play a role in both of them. Decompression leads to a fresh set of stresses in the tablet as a consequence of elastic recovery, which is aided by the necessary pressures to eject the tablet from the die. To resist these additional pressures, the tablet must be mechanically robust; otherwise, the risk of structural failure would rise (Hiestand, et al., 1977; Rees & Rue, 1978).

**Compaction simulator**

These systems provide smart tablet press technology as well as powder analysis and formulation software development options. They were created as a result of the scarcity of accessible pharmacological ingredients throughout the formulation and process development stages. The difficulty to utilize full-scale rotary presses because they need huge quantities of powder to fill the feed frame and run the compaction under steady-state circumstances also led to the development of the compaction simulator (De Boer, et al., 2004; Garekani, et al., 2001).

The aim is to create new research hardware and software on a continual basis to aid compaction simulation of industrial production cycles, powder characterisation and formulation services, compression, and material sciences in the pharmaceutical, food, and

cosmetics industries. The formation of powders may be aided by a thorough knowledge of the compaction process.

It is basically a device that is able to mimic the real-time exact tabletting cycle and also able to record the parameters. It is a new aspect of tabletting research and is done to investigate power compaction behaviour and fundamental material characterization by utilizing a variety of compression parameters like compaction force and punch displacement (Reugger & Celik 2016). Compaction simulators can generate upper and lower punching displacement profiles, which may be used to get information about the powder's compaction behaviour.

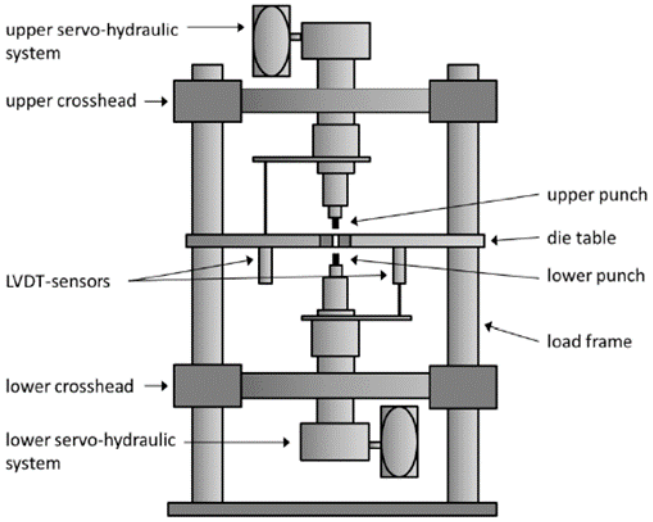
A compaction simulator is considered to be a multifunctional instrument that could help in all the phases of drug production and development (Celik, 2016; Celik & Marshall, 2010; Michaut et al., 2010).

DC Paracetamol powders were directly compacted by using the compaction simulator (Stylcam 200R). It is also called a Mechanical compaction simulator that resembles a hydraulic compaction simulator's design. It is made up of a single punch system where both the upper and lower punches are separately driven by hydraulic rams, which in their turn are controlled by a computer. The machine is capable of mimicking the exact cycle, including any tabletting process in real-time and is able to record all the critical parameters during the cycle (Çelik and Marshall., 1989).

***Hydraulic compaction simulators.*** Hydraulic compaction simulators are a group of these specifically built instrumented machines. The hydraulic force is the primary deriving force for compacting the tablets, as the name implies. The simulator comprises of two separate servo-hydraulic systems that drive upper and lower punches, crossheads for punches, the die table and its supporting column, and the remainder of the load frame, all of which are controlled by a computer. The simulator's construction is shown in (Figure 2).

Figure 2.

*Schematic representation of a hydraulic compaction simulator (Fonteyne, et al., 2013)*




In order to carefully control and obtain insight into the compression process, sensors, load cells, and multiple control mechanisms are implemented in the simulator. Hydraulic system, crossheads, fill depth and ejection height are all contributing to determining the force and movement of the punches. Load cells on the lower and upper punches measure the conduction of force exerted on the powder bed by linear variable displacement transducers (LVDT sensors). Load cells on the lower punch can also determine the ejection force. Third generation compaction simulators include additional features such as measuring the take-off force (ESH powder compaction simulator) and measuring internal tablet temperature at the time of compaction and tablet formation (Merlin compaction simulator).

Hydraulic systems are used by hydraulic compaction simulators to mimic the compression cycle for any desired shape. There are two main mechanisms in which the simulation can be accomplished load control (the force) or position control (movement of the punches). The load control method is used for mimicking the force-time profile of machine production, but compaction simulators are rarely used for this purpose. On rotary tablet press, there are multiple factors that influence the force-time profile like tooling, the geometry of the machine, material under compression, and tabletting speed. These factors cannot be theoretically calculated or programmed into the simulator. Data from a

production press and be collected by instrumented punch and can be applied in the compaction simulator, but the data is limited to a certain punch size and shape, and the calculations are not clearly identified. Moreover, mostly there is insufficient material in the early stages of drug formulation to run the product on a rotary tablet press from the collection of the data and to transfer it to the compaction simulator.

Position control is a frequently used method in which the movement of the punches is forced to be in the same design during the production press leading to the force-time curve to follow automatically (Kachrimanis, et al., 1998).

In the investigation of the punch movement, there are three available methods. Firstly, reviewing and usage of any pre-recorded data from any tablet press. Secondly, artificial punch displacement profiles can be used. “Single-ended” profile (stationary lower punch) and “sawtooth” profile (constant displacement speed) were used as examples in compaction studies. Finally, the administration of theoretical profiles can be calculated for the press and punch geometry as well as tabletting speed (Vercruysse, et al., 2012; Peeters, et al., 2015). In order to induce punch action in a tablet press, the resultant sinusoidal equation is utilized. Hydraulic compaction simulators are not recommended to be used for simulation of high-speed production processes, scaling-up experiments or troubleshooting due to the restrictions regarding pre-recorded data usage and the inconsistencies between artificial and theoretical profiles from a compaction simulator and the actual profiles on a rotary press.

However, they are preferable in basic compaction research and material characterization because of the accurate results they generate with just a small amount of material required. Many independent parameters can be modified and controlled, which makes these simulators versatile tools for basic compaction research (Vervaet & Remon, 2005; Q8 (R2) Pharmaceutical Development, 2009).

***Mechanical compaction simulators.*** A second group which is called mechanical compaction simulators, depends on either load control (the force) or position control (movement of the punches) without employing any hydraulic systems. The first type of mechanical compaction simulators is the Presster$^{TM}$, the linear mechanical rotary tabletting machine simulator (MCC, New Jersey, USA). The movement of a single pair

of punches could be described as linear movement forth and between the compression wheels on the upper and lower punch track. Matching the diameter if the compression rollers can simulate the production press geometry. Also, other factors could be controlled mechanically, such as controlling the fill depth to regulate tablet weight and the distance between rollers to control thickness and force (Kirsch & Drennen, 1999). Standard instrumentation makes it easier to monitor upper punch power, upper and lower punch movement, and compaction speed. If required, pre-compression rollers, lower punch force, take-off forces, radial die wall pressure, and an ejection cam with changed angle and ejection force monitoring may all be included in the simulator.

Mechanical compaction simulators are constructed similarly to hydraulic compaction simulators. In contrast to hydraulic systems used in hydraulic compaction simulators, the load frame bears the upper and lower punches with the die table, and the punches' movement is limited to the vertical direction. Stylcam (Medelpharm, Beynost, France) uses electrically powered cams to control the movement of the punches.

These cams are positioned underneath the bottom compression wheel and may simulate various compaction simulators and dwell durations owing of the varied acceleration speeds of the punches. It is considered a simulation of pre-compression when the tablet is compressed twice. Other compaction simulators may be compared to the instrumentation (Carr, 1965; Fonteyne, et al., 2012) “tabletting robots” is the name referred to the latest designs of these simulators.

They may have the same characteristics as other mechanical compaction simulators, but they can also include up to three feeders for 5-layer tablets, a feeder for core tablets for compression coating, specific tooling fill, forced feeder, and uniaxial and biaxial punch movement capability. Furthermore, with a maximum output of 1200 tablets/hour, these simulators are perfect for clinical production batches. Mechanical compaction simulators replicate the tableting process on rotary tableting machines more than hydraulic compaction simulators. Some systems, however, are untrustworthy. The die filling phase, for example, is virtually difficult to replicate or reproduce on a linear (stationary) single-punch machine, even with a mix of suction, gravity, forced, and centrifugal forces. The most significant benefit of this kind of mechanical compaction

simulators in early stage formulation tests is the minimal quantity required of the product, which makes them a unique instrument.

**Mathematical models of powder compression.**

According to the literature, many efforts have been made to develop a compression model based on a physical knowledge of the powder compression process (Sonnergaard, 2001; Çelik, 1992), and from which of the compression parameters the reflects the main built and characteristics can be retrieved.

Taking the whole powder bed into consideration along with a tablet during modelling by relating powder porosity or volume to the pressure applied is the dominating approach. Logarithmic changes of both the porosity or volume terms and the pressure term are frequent. Such a relationship is firstly reported and proposed by Walker in 1923 (Walker, 1923). Then, in recent days, more advanced models have been proposed with the involvement of computational techniques.

One of these models is The Discrete Element Method (DEM) which is a advanced determination technique that considers the system existence modelled on a microscopic level, where the physics of separate powder particles can be controlled (Roberts & Rowe, 1987; Bassam, et al., 1990; Hausner, 1967). Another one is The Finite Element Method (FEM) that basically involves a macroscopic view of the system existence modelled (Eriksson & Alderborn, 1995).

It is worth mentioning that both of these models can be used in conjunction together, so the usage of one of them does not prevent the usage of the other. For the pharmaceutical area, the models of Heckel and Kawakita has been broadly and often used because of their simple mathematical form and also the fact that generous information as of now has been based on data relied on them. Most importantly, both Heckel and Kawakita equations are considered to be attractive when it comes to the physical significance of the compression parameters.

The main aim of both of these equations when describing powder compression is the abstraction of the particle characteristics quantitatively in the form of an equation to increase the compression process understanding. As they are mathematical equations, they require known variables to be practically applicable. These variables consist of pressure

and quantitative measurement of the distance between powder particles (i.e. density, porosity, volume, powder bed height etc.).

There are two opposing perspectives in which a compression equation can be developed. Firstly, extraction of single powder properties from bulk powder behaviour which has been done by Heckel (Kaye, 1967; Nicklasson & Alderborn, 2001), and Kawakita (Eriksson, et al., 1993), whose equations are called after their own names. Secondly, deriving bulk powder behaviour from single-particle properties, which was done by Adams (Alderborn, et al., 1985; Klevan, 2011).

Although the variables in the Heckel and Kawakita equations have different units, they both describe the same process, which is how distance is made when force is applied. The difference between these two equations is that the Kawakita equation describes the closeness of powder particles as a function of degree of compression as a function of applied pressure, whereas the Heckel equation describes the closeness of powder particles as a function of porosity as a function of applied pressure.

***The Heckel Equation.*** In the beginning, Shapiro and Konopicky published a powder compression study, where they used the natural logarithm of the tablet porosity as a function of the applied pressure for describing the process ( (Konopicky, 1948). However, from 1961 and after Heckel Equation became the most frequently used and well-known equation (Heckel, 1961). The original name of the equation is Shapiro-Konopicky-Heckel equation, but it has been referred to as the Heckel equation in this study for the sake of simplicity.

This equation is built on the assumption that powder compression resembles a first-order chemical reaction, where the reactants are the pores (voids between particles), and the product is bulk densification. The equation was applied to material that has a predominant plastic deformation like metal before its application on pharmaceutical powder**.**

$$\ln \frac{1}{E} = kP + A \qquad \text{Equation 1}$$

Where $E$ is the porosity of the powder bed and $P$ the applied compression pressure, $A$ and $k$ are parameters.

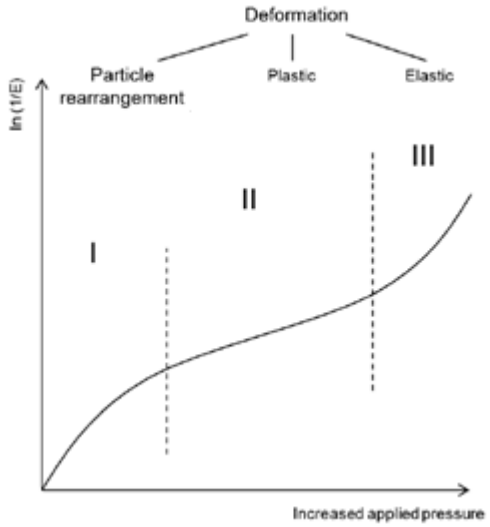
Three different regions distinguish the Heckel profile as shown in (Figure 3), beginning with a non-linear segment (Region 1), then a linear segment (Region 2), and lastly, a non-linear segment (Region 3). Each one of these regions is expressed with the underlying controlling compression mechanism that dominates the region. In the first region, the dominating controlling mechanism is explained in the literature as particle rearrangement during compression (Heckel, 1961; Shapiro, 1997).

For the second region, it is usually accepted that either plastic or elastic deformation is the controlling mechanism. Regarding the third region, an argument occurred about that elastic deformation of the compacted powder particles controls the process (Sun & Grant, 2001). Low-pressure densification is reflected by inter particulate motion; this reflection is indicated by the A parameter in the Heckel equation.

The inverse of the slope (parameter *K*) is calculated from the linear segment. This is referred to as the yield pressure (*Py*) or Heckel parameter, which is common for the indication of the hardness or plasticity of a particle.

Figure 3

*Schematic illustration of the three different regions dominating the Heckel profile (Ghori & Conway, 2016)*




In the literature, there are differences between reported values for the Heckel parameters. Those differences might be a result of the way of determination of the linear segment, data acquisitions accuracy, or deviations in true densities that have been measured. Negative porosities in the upper-pressure part of the profile are also reported.

This may result in virtually reduced recovered Pys and thus contradict the notion that particle density remains constant throughout compression (Sun, 2006; Sonnergaard, J. M., 1999; Sonnergaard, 2000).

***The Kawakita equation.*** Kawakita equation is another form of compression data representation that relates the volume decrease of a powder bed to the applied pressure (Kawakita & Lüdde, 1965; Kawakita & Lüdde, 1971).

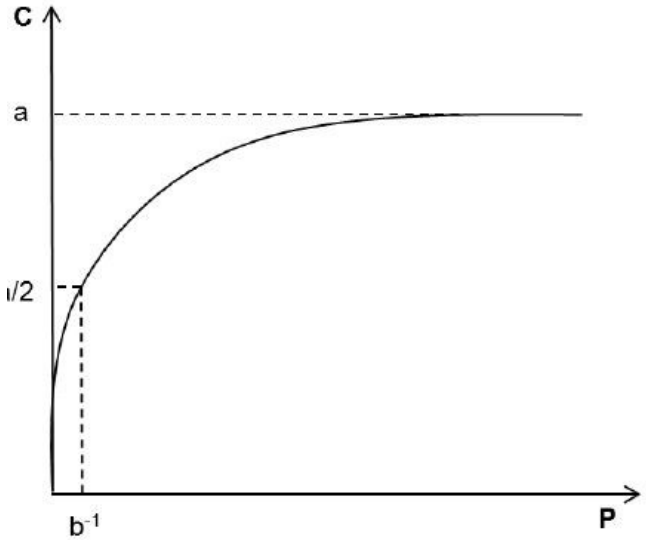
$$\frac{P}{C} = \frac{1}{ab} + \frac{P}{a} \qquad \text{Equation 2}$$

Where $C$ is the degree of volume reduction. $c = \frac{Vo-V}{Vo}$, where $Vo$ is the initial volume of the powder bed, and $V$ is the volume under applied pressure), $P$ is the applied pressure, $a$ and $b$ are parameters.

It is possible to derive the values of $a$ and $b$ parameters by using the linear relationship between $\frac{p}{c}$ and $P$. the maximal engineering strain ($C$ max of the powder) is represented by parameter a, while parameter b is mathematically equal to the reciprocal of the pressure when (C=$C$max/2), as illustrated in (Figure 4).

Figure 4

*Schematic illustration of a typical engineering strain – pressure –curve and mathematical interpretation of the Kawakita parameters (Comley, 2010)*



In the analysis of soft, fluffy powder that is compressed under low pressure, the Kawakita equation is the best choice (Denny, 2002). However, for a large extend influence of the parameters outcome retrieved, the consideration of location the start volume for the calculations is an essential point (Sonnergaard, 2000; Kawakita & Lüdde, 1971). Fracture strength of single particles, the plasticity of a granule, or the agglomerate strength is thought to be imitated by the inverted b parameter, which is present in the discussion of the physical interpretation of the Kawakita parameters in the literature (Yap, et al., 2008; Adams, 1994; Nordström, et al., 2008).

The physical interpretation of the b parameter regarding bulk powders has been a lot more complex to represent resistance against compression. In the tapping of bulk powders, the Kawakita equation also could be applied as a measure of cohesion and fluidity by putting the tapping number (N) instead of the pressure (P) in the equation (Yamashiro, et al., 1983; Yu & Hall, 1994).

As to the physical significance of the Kawakita parameters, parameter (a) still stands for the greatest degree of volume reduction currently at endless tapping and is considered to correlate to fluidity. The inverted b parameter is viewed with inter particulate cohesiveness because the b parameter reflects the tapping capacity.

**Factors Affecting Compression and Tablet Quality**

***Surface Properties.*** Powder flowability and attraction forces between molecules are majorly influenced by the surface properties of powder material. Ions at the surface are distinguished from the ones present within the particle itself by a different intermolecular and intramolecular distribution. Because of unsatisfied attractive molecular forces that expand out beyond the solid surface, leading to the creation of free surface energy which has an important role in the interaction between particles (Booth & Newton, 1987).

Constituent the appealing powers oppose the differential development of constituent particles when exposed to an outer power. Different kinds of resistance from relative movements of particles incorporate the residual solvent, adsorbed moisture, and electrostatic forces on the outside of strong particles (Marshal, 1987).

***Particle Shape.*** Spherical-shaped granules are desirable because they have better compression and flow characteristics than other granular shapes. Methods such as high-shear granulation, spray drying and fluid bed granulation could result in nearly spherical–shaped granules (Mosharraf & Nyström, 1995).

***Bulk and Tap Density.*** The density of a movable powder in a die is defined as bulk density. It is preferable to get the highest bulk density possible. After applying a pre-decided number of tapping or vibration condition to the loose powder, the density of this powder is called tap density (Astm, 2006). Tapping or vibrating the powder mains to particle rearrangement and reduction of the voids in the microstructure, which eventually will cause the tap density to be lower than the bulk density.

***True Density.*** True density is the density of the solid material without the volume of either closed or open pores. The true density may match the theoretical density of the material Depending on their molecular arrangement, which might be an indicator for the spacing between particles and how near the material is to a crystalline state or the proportions of a binary combination. True density measurements may be done on APIs, excipients, mixes, and monolithic samples such as tablets (Sun, 2006).

***Flowability.*** Flowability of a powder in the pharmaceutical industry is essential to accomplish a proper substantial of the die during the compression process. The flowability of a powder can commonly be measured in two ways, Hausners' ratio and Carrs' index. Hausners' ratio is the percentage between tapped density and loose-packed bulk density of powder, while Carrs' index is the ratio between tapped density and bulk density of a powder which illustrates the compressibility of powder particles (Hausner, 1967; Grey & Beddow, 1969).

The equations below give detailed information about how can we obtain Hausner's ratio and carrs' index. The table below (

Table 1) shows an explanation of Hausners' ratio and Carrs' index values where A Hausners' ratio of <1.25 indicates a powder that is free-flowing, whereas >1.25 indicates

poor flowability. The smaller the Carrs' Index, the better the flow properties. For example, 5-10 indicates excellent, 11-15 good, 16-20 fair and > 23 poor flow.

$$\text{Carrs' index} = \left(\frac{P\ tapped - P\ bulk}{P\ tapped}\right) \times 100 \qquad \text{Equation 3}$$

$$\text{Hausners' Ratio } = \left(\frac{P\ tapped}{P\ bulk}\right) \qquad \text{Equation 4}$$

Table 1.

*The Compressibility Index and* Hausners' *Ratio Ranges (Taylor & Aulton, 2013)*

| Carrs' Index (%) | Flow Character | Hausners' Ratio |
|---|---|---|
| **≤10** | Excellent | 1.00–1.11 |
| **11–15** | Good | 1.12–1.18 |
| **16–20** | Fair | 1.19–1.25 |
| **21–25** | Passable | 1.26–1.34 |
| **26–31** | Poor | 1.35–1.45 |
| **32–37** | Very poor | 1.46–1.59 |
| **>38 Very** | Very, very poor | >1.60 |

The angle of repose (

Table 2) is also used to measure the flowability of powders and defined as the maximum angle (θ) between the plane of powder and horizontal surface.

Equation where (h) is the height of the mound formed when the powder is allowed to fall through a funnel and (r) is the radius of the mound calculated by using a graph paper (Geldart, et al., 2006)**.**

$$Angle\ of\ Repose\ (\theta) = \tan^{-1}\left\{\frac{h}{r}\right\} \qquad \text{Equation 5}$$

Table 2.

*The Angle of Repose Ranges for Powder Flowability* (Geldart, et al., 2006)

| Flow Property | Angle of Repose (Degrees) |
|---|---|
| **Excellent** | 25–30 |
| **Good** | 31–35 |
| **Fair—aid not needed** | 36–40 |
| **Passable—may hang up** | 41–45 |
| **Poor—must agitate, vibrate** | 46–55 |
| **Very poor** | 56–65 |
| **Very, very poor** | >66 |

***Particle Size Distribution and Grading.*** When the space and voids between the largest particles are filled with smaller particles, the highest density for a loose powder could be obtained. The voids between smaller particles are filled with even smaller particles. This is referred to as particle size grading. Particle size grading and distribution contribute to gaining proper particle packing that improves tablets quality. However, the size segregation phenomenon, which is undesirable, could be promoted by broad particle size distribution (Razavi, et al., 2018).

***Granulation Method.*** Usually, Granulation is done to the pharmaceutical powders before tablet manufacturing because of their poor flowability and compaction behaviour. For the making of cancellous and free-flowing granules, the optimal granulation method is selected. This allows the production of tablets with maximum mechanical strength using low compression pressures (Vercruysse, et al., 2012).

***Moisture Content.*** In agglomeration, the most commonly used liquid is water and maintaining the amount added in a narrow range is essential because of the high sensitivity of granule growth to the amount of liquid in the system. The spread of the particle size

distribution affects the moisture content favourable for granulation (Stanley-Wood, 1990).

***Lubricants.*** The lubricant is a surfactant that efficiently reduces friction between the powder and the die wall and is also highly absorbed. High adhesion strength and low shear strength are critical properties of effective border lubricants. (Reed, 1995).

***Binders.*** Binders which are organic chemicals, are incorporated into particle assemblies in order to induce size enlargement. Binders could contribute significantly to the bond strength in the form of either a film, matrix or chemical types. The granule produced is affected by binders in the mechanism of agglomeration and the granular distribution in the agglomerate. The binders tend to be equally distributed throughout the granule in wet massed agglomerates, while in spray-dried material, the binders are highly concentrated at the surface shell (Stanley-Wood, 1990).

***Plasticizers.*** For the modification of the viscoelastic characteristics of a condensed binder phase fil on the particles, a plasticizer is added. Moulding of the power systems, which contains a binder beyond the glass transition temperature of the binder, is generally done. Small plasticizing molecules affect the binder by softening it and increasing its flexibility, but also it reduces its strength. Glass transition temperature of the binder is effectively reduced by the plasticizer (Reed, 1995).

**Improvement of Compaction Behaviour**

Poor compressibility is considered to be an issue for several pharmaceutical drug powders and excipients. The priorities should be set to improve the compaction behaviour of the API or the excipient(s) depending on the material that constitutes the majority of the mixture. Furthermore, co-processing and granulation may be needed in order to produce the desired compatibility. Regarding low dose drugs which have poor compatibility, tabletting problems rarely occur because excipients play a major role to fulfil the required compressibility.

However, in high dose drugs, tabletting problems have a higher risk to occur, so in this case, the selection of excipients and specifically binders and diluents with or without the improvement of the API is of high importance for minimizing the tabletting problems.

***API Modification.*** The limited role of excipients in high dose drugs lead to the other option of enhancing and improving the high dose drugs compaction behaviour, which the modification of the API. The API modification is always acceptable or permissible (Mohan, 2012).

***Excipient Modification/Selection.*** The quality attributes of a certain tablet could be prejudiced by the type and the volume of the excipient(s) selected. Excipients are classified according to their role in compaction as follows: firstly, excipients that have a positive influence, such as binders and diluents. Secondly, excipients that have a negative influence, such as lubricants and disintegrants (Bolhuis & Anthony Armstrong, 2006).

***Diluents.*** Because of their greater availability among other excipients, the diluents considered to play the most essential part compared to other excipients. Some of the diluents could be referred to as highly compressible such as MCC, and other diluents could have low compressibility, such as starch.

Knowing that the main behavioural designs of pharmaceuticals while compression is applied are elastic, plastic deformation, and brittle fractures, the exhibition of a upper number of forces that leads to higher compact strength is a characteristic of materials that have plastic deformation properties such as MCC and amorphous binders. Even in the absence of fragmentation, compact strength is highly influenced by the rough surface of the particles (Carlson & Hancock, 2006).

Therefore, the optimum balance between plastic behaviour and brittle fracture is the base of successful tablet production as indicated by API and excipients compression characteristics. The most frequently used excipients listed according to their brittleness from low to high as follows: MCC, spray-dried lactose, β-lactose, α-lactose, α-lactose

monohydrate, and DCP (Nyström, et al., 1982). Co-processing has been rising and getting more popular in the generation of directly compressible excipients.

***Lubricants.*** Lubricants, as other classes of pharmaceutical excipients, are used with the aim of ensuring an appropriate final product quality which is done by adding the lubricants to solid dosage form formulations. Lubricants are referred to as the best friction reducing agents that happens between two rubbing surfaces. The optimization of lubricant concentration in the formulation is of high importance in order to minimize dissolution and tensile strength problems, which could be done by establishing an ejection profile for each lubricant to decrease tablet compaction stresses (Enneti, et al., 2013).

The greatest frequently used lubricants include water, stearic acid, insoluble metallic stearates, waxes, and talc. Furthermore, there are also water-soluble materials like sodium benzoate, sodium acetate, boric acid, leucine, sodium chloride, sodium oleate, and sodium lauryl sulfate.

***Disintegrants.*** In order to obtain the required dissolving rate of the drug ingredient, it is necessary to overcome the cohesive strength of a tablet and split it into fundamental particles. This is why disintegrants are included in formulations. Yield is a negative impact on tensile strength when disintegrants swell by taking moisture from their surroundings. Several frequently used diluents, such as MCC and starch, have disintegrant properties. As previously stated, MCC has a higher compressibility rate than starch, and both influence compaction tensile strength. Many super-disintegrants are used in a way in which they can act at lower concentration and have a lower probability of changing the compaction behaviour. Examples of these super-disintegrants are rospovidone, coscarmellose, and sodium starch glycolate. However, a reduction of the tensile strength in the tablet as a consequence of poor compressibility is noticed when sodium starch glycolate is at above 10% of concentration.

Therefore, an optimization of the disintegrant concentration is needed to dodge their negative effect on the tablet blend's compressibility. The most commonly used disintegrants involve MCC (5–15%), starch (3–15%), pregelatinized starch (5–10%), croscarmellose sodium (1–5%), sodium starch glycolate (2–8%), and crospovidone (2–

5%). Swelling is the basic mechanism of disintegration in the presence of water (Desai, et al., 2016).

***Granulating Agents/Binders.*** Granulating agents are essentially used in the formation of granules from the powder. Organic solvents and also water could be considered as granulating agents in which they can dissolve the surface of the particles and form bonds upon evaporation. However, these kinds of bonds are considered to be weak and result in friable granules formation. So, a binder is added to the formulation to improve the strength of the granules and resist capping and lamination problem.

The granulating agents are known to be hydrophilic cohesive polymers that help in the granulation procedure and impart strength after drying. Increasing the elasticity occurs when a binder is added, which leads to a reduction of the tablet strength as a result of breaking the bonds when the compaction pressure is released (Nyström, et al., 1982).

For this reason, complete awareness of the binder properties for improving the tablet strength and also the knowledge of the interactions between tablet constituents are required to decide and select which is the most suitable binder to use.

Granulation can be explained as the adherence of powder particles with each other to form larger objects (granules) by physical means. The size of pharmaceutical granules ranges depending on their aim of use, between 0.2 to 0.4 mm.

Granulation is done most frequently in the production and manufacturing of tablets and capsules. It is worth mentioning that even though the typical granular size is between 0.2 to 0.4 mm, the granular size could be larger if the granules are going to be used as a dosage form itself (Shanmugam, 2015).

*Purpose of granulation*. Apart from costing more money, many benefits could be gained through the granulation process, such as improvement of the flowability and the compaction characteristics of the mixture, prevention of segregation of constituents in the powder mixture, and the reduction of dusting while handling the powder which is considered to put a person who directly contacts with the powder in risk (Cantor, et al., 2008).

***Wet granulation:*** Granulation is the process in which minor particles are combined together to form agglomerates that are called granules. It is a must to add adhesive substances called granulating agents (binders) within the formulation to achieve cohesion between the particles. Wet granulation is the most commonly used type of granulation in the pharmaceutical industry. It includes liquid solution addition (with or without) to powder to create a wet mass, or it could form granules by adding an adhesive to the powder mixture (Lachman, et al., 1986). Following the formation of wet masses, they must be dried and sized to yield granules. While wet, the moist powder particles are held together by a mix of capillary and viscous forces. Extra permanent linkages are formed during the drying processing, resulting in the formation of agglomerates.

The advantages of conventional wet granulation process include: improvement of flowability and compressibility and increasing the granular density, reduction of dust hazards, prevention of powder segregation, enhancement of colour distribution and soluble drugs if they were added to the binding solution and increasing the hydrophilic characteristics of hydrophobic surfaces (Parikh, 2016).

The disadvantages of the conventional wet granulation process include: high process costs (due to the need for space, special equipment, time, and energy), material loss during several stages of processing, processing complexity, aggravation of any incompatibility between formulation components during processing, and Moisture-sensitive or heat-labile drugs are not suitable choices (Ofoefule, 2002).

There are three essential stages for the conventional wet granulation process (Iveson, et al., 2001)

*1-Wetting and nucleation.* In the granule manufacturing process, this is the first and most important step. To generate nuclei, the granulating fluid first wets the powder bed and existing granules. In contrast to mechanical mixing, spray rate or fluid dispersion, as well as feed composition characteristics, have a significant effect on this stage. The wetting stage is inextricably tied to the nucleation process, or the initial coalescence of primary particles in the immediate region of the big wetting drop (Ofoefule, 2002).

*2-Growth and consolidation.* During the ball development stage, partially wetted primary particles and bigger nuclei combine to create granules made up of several particles. Coalescence is a broader term for the successful collision of two granules,

resulting in the formation of a new, larger granule. Compaction forces caused by bed agitation consolidate granules as they grow in size. The degree of consolidation is determined by the granulation equipment's agitation and the granules' resistance to deformation. Internal granule porosity, and hence final granule attributes such as granule strength, hardness, or disintegration, are controlled during this phase of granule development (Ofoefule, 2002).

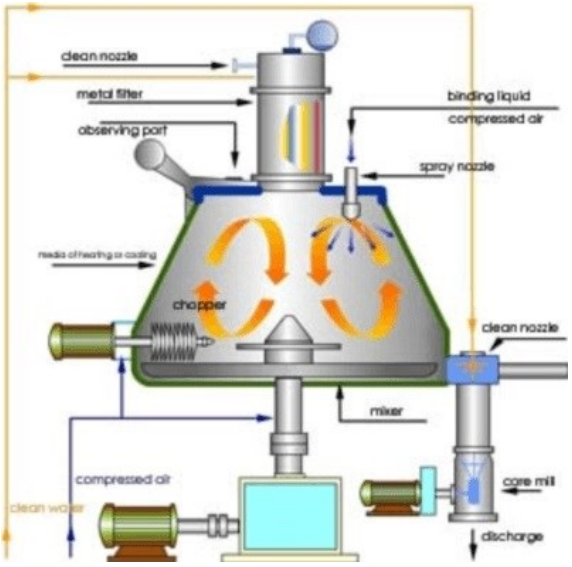
*3-Breakage and attrition.* Formed granules shatter into fragments at this phase, which binds to neighbouring granules to produce a material coating over the surviving granule (Parikh, 2016).

**Wet Granulation Techniques:**

*1-High shear mixture granulation (*Figure 5*).* In the pharmaceutical industry, high shear mixtures are commonly employed for blending and granulation. An impeller rotating at high speed sets the particles in motion in this sort of machinery (Approx 50-100 rpm). A chopper, which rotates at 1500–4000 rpm, is also included in the equipment (Parikh, 2016).

Figure 5

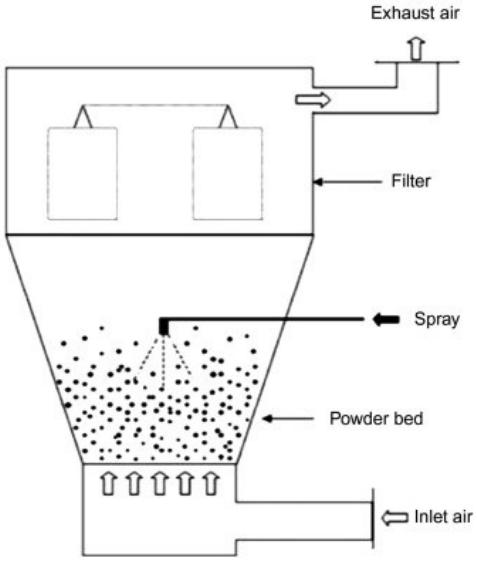
*Schematic representation of a High Shear Mixer Granulator and process*



*2-Fluid bed granulation (*Figure 6*).* Fluidization is the process of converting fine particulates into a fluid-like condition by contacting them with gas. The fluid will support the particles at a specific gas velocity, allowing them to move freely without being entrapped. Fluid bed granulation is a single-equipment granulation technique that involves spraying a binder solution onto a fluidized powder bed (Patel, et al., 2007).

Figure 6

*Schematic representation of Fluid Bed Granulation and process*




***Dry granulation:*** Because the product may be sensitive to moisture and heat, dry granulation comprises forming granules without the use of a liquid solution. Dry powder particles can be mechanically compressed into slugs or rolled into flakes in this technique. Unlike using a liquid in wet granulation, in dry granulation, high pressure is used in the aggregation of the powder particles. Mostly, this is done by means of two different methods. The first method consists of using a heavy-duty tabletting press to produce a large tablet (slug). The second method is to pass the powder between two rollers (roller compaction) after compressing it, which will eventually result in sheet formation. Using a mill, the large aggregates resulted from both methods are broken into small granules. Finally, the granules are sieved in order to get the desired size fraction suitable for tablet formation (Kleinebudde, 2004)

### *Quality Control Tests*

**Weight Variation.** A technique for ensuring that each tablet has the correct amount of API. The volume of material that fills the die in the pressing machine determines the weight of the tablet. The tablet weight is determined once the excipient measurements have been determined. Random tablets are pulled out of the production process to be weighed and evaluated for appearance. Only 2 tablets out of a total of 20 may be outside the percentage range, and not more than 2 times the percentage limit. (Table 3) shows the tolerance of weight variation for the tablet dosage form (USP 35, 2011)

Table 3.

*Describes the Tolerance of Weight Variation for the Tablet Dosage Form*

| Average Weight of Tablet, mg | Percentage Difference |
|---|---|
| 130 or less | 10% |
| From 130 through 324 | 7.5% |
| More than 324 | 5% |

**Hardness.** The resistance of a solid to permanent local deformation is the definition of hardness (Tabor, 1951). Giving by (Leuenberger & Rohera, 1986). Hardness is primarily related to plasticity assessment to a number of essential material properties. It is generally measured by an indentation test. Hardness testing methods are divided into two groups by Leuenberger and Rohera: the first is using the static impression method to determine hardness level, which is most commonly used, while the second is using a dynamic method in hardness determination. The ratio of the load to the diameter of the indentation is an expression for the Brinell Hardness Number (BHN), which can be calculated by the following equation:

$$BHN = \frac{2F}{\pi D\left(D-\sqrt{D^2-d^2}\right)} = \frac{2F}{\pi Dh} \qquad \text{Equation 6}$$

Where F = Indentation Force, D = diameter of indenter, d = diameter of indent, h= depth of indentation

**Friability.** Friability is defined as the measure of the tablet's confrontation to subsequent process condition and transportation. In other words, it measures the ability

of a tablet to withstand the attrition forces during different periods such as production, handling, transportation, and storage to be accurate and certain about the amount of drug administered.

This measurement is done by mimicking the forces that may be applied on the tablets during the previously mentioned conditions. This is done by using a rotating wheel or drum known as friabilator.

This drum has a specific diameter and depth with a single removable side. One percent of weight loss is the maximum limit of loss accepted for uncoated tablets (European Pharmacopoeia, 7th edn, 2011). The tablet is referred to as friable when it mechanically erodes during handling (Uddin, Mamun, Tasnu, & Asaduzzaman, 2015).

**Disintegration time.** A disintegration time test is done to assess the time needed for a tablet or a capsule to be disintegrated when they are located in a liquid medium. This test is important to know the tablet's availability for absorption, disintegration and liberation, and the dissolution of the active pharmaceutical ingredient into the body fluids.

If a certain drug product passes the disintegration time test without crossing its limits successfully, this will not assure a complete efficacy of the drug. However, if the disintegration time for a drug product were not within the accepted limits, this will certainly assure the failure of the drug product to deliver the desired effects. The test is done using the disintegration apparatus that is consisted of six chambers, where it has cylindrical tubes that are opened on one end while it is closed by a mesh screen on the other end (Hymavathi, et al., 2015).

### *Introduction to QbD*

Manufacturing processes in the pharmaceutical industry were developed using experience knowledge bases. A rise in the number of necessary materials, efforts, and expenses associated with the drug licensing process has been matched by an increase in the pharmaceutical industry's complex methods and risks. (Woodcock, 2004).

Obstacles connected to drug manufacturing, which raise the risks of drug development, are extremely troublesome to remove. As a result, proper complexity and

risk management, as well as decision-making process regulation, are required. New current tools have been designed to be the best at building quality in pharmaceutical products, as well as to provide a solution to cost, material, and difficult manufacturing process concerns. One of these newly developed tools is Quality by design (QbD).

QbD is a new concept for pharmaceutical products quality development which became a cornerstone involving a method development with good process understanding and risk- and science-based product (Lawrence, 2008).

The main objective in QbD is to design quality into products as an alternative to testing the quality of the finishing product after the manufacturing process. The reproduction of profound process understanding is possible now, thanks to advanced modelling and simulation and process analytical technology (PAT), leading to an increased possibility of robust manufacturing processes creation. International Conference on Harmonization (ICH) Q8 guideline was published in May 2006 for pharmaceutical product development where firstly QbD was revealed and identified as "a systematic approach to development that begins with predefined objectives and emphasizes product and process understanding and process control, based on sound science and quality risk management"(ICH, 2008; Gochhayat, et al., 2019).

Q8 guideline has been accompanied by the followed publication of ICH Q9 that describes the main principle of quality risk management that should be applied to different sides and aspects of drug quality (ICH, 2005).

ICH Q10 is considered to be an inclusive approach which creates built on the International organization for standardization (ISO) concepts, an effective pharmaceutical quality system. It also involves the regulations of Current Good Manufacturing Practice (cGMP) of ICH Q8 and ICH Q9. "Development and manufacture of drug substances" is the title of the ICH Q11, which was aimed for the active ingredients committee, and it is under progression at the current time (Moy, 2009; Guideline, I. H. T., 2011).

**Benefits of QbD.** QbD can provide several benefits in different aspects of pharmaceutical industry. Firstly, from manufacturer and manufacturing view it could help in increasing the understanding of the product, the processes involved in manufacturing, and the effects of active ingredients and excipients on manufacturing,

leading to a creation of more efficient processes, development of less problematic design, solving technical issues and keep a continuous development and improvement in product and manufacturing processes.

It also can decrease the variability in the project, manufacturing total cost, quality costs, wastes and losses, and the number and complexity of analysis tests. All of these benefits have a certain aim which is delivering the most efficient drug possible with the highest quality and lowest possible cost and the least time. (Woodcock, 2004; Lionberger, 2008).

Secondly, from licensing view, the QbD approach recommends licensing flexibility when applied to not only previously manufactured products but also on studies of biotechnological studies that recommend a design space. The well-understood processes contribute to a shortening of the approval time and decreasing the number of audits. Moreover, the studies that include a design space are facilitated by several terms that are explained in ICH Q8, such as Applying new technologies without the licensing consent, faster approval and facilitation during the audit, reaching a scientific agreement between industry and authority, and lessening the required manufacturing supports for post-licensing changes (Nadpara, et al., 2012).

Finally, operational strategies are enhanced and benefited the QbD approach. These benefits are as follows: most recent and modern technologies are used in manufacturing, the quality level is guaranteed and increased from unit to unit, risk reduction, real-time data collection, better information management and fewer documents number, and accomplishing a more convenient overall work model (Jain, 2104).

**Elements of QbD.** While developing a new pharmaceutical product by using the QbD approach, the critical quality characteristics from the patient's perspective should be identified and explained into the critical quality attributes (CQAs) by the applicant and eventually introduce the relation between CQAs and formulation/manufacturing factors to constantly provide a drug product with the identified CQAs to the patient.

QbD includes multiple elements, which are as follows: Firstly, a quality target product profile (QTPP) that sets up the main principles for the critical quality attributes (CQAs) of the drug product. Secondly, identification of critical material attributes

(CMAs) alongside product design and comprehension. Thirdly, identification of critical process parameters (CPPs) followed by linking CMAs and CPPs to CQAs according to scale-up principles and risk assessment process. Fourthly, controls for each step of the manufacturing process along with a control strategy consisting of optimal ideals for the drug substance(s), excipient(s), and drug product. Finally, consistent process competence and continuous improvement (Aksu & Mesut, 2015).

**QTPP.** QTPP is a start-up line of the QbD approach, which is essential in creating a foundation of the design for product development. It is defined as "a prospective summary of the quality characteristics of a drug product that ideally will be achieved to ensure the desired quality, taking into account the safety and efficacy of the drug product" (Lawrence, et al., 2014). There are several considerations in QTPP which involves dosage form, delivery systems, administration, dosage strength container closure system, attributes affecting pharmacokinetic characteristics (aerodynamic performance and dissolution) and therapeutic delivery or release which are suitable to the developing drug product dosage form, and the criteria of the drug product quality (purity, sterility, stability, and drug release) (Riley & Li, 2011).

QTPP identification is of high importance before the actual beginning of the development, and insufficient information with a lack of a satisfactory QTPP lead to the loss of time, financial resources, and material used in the development. In contrast, a good understanding and enough information indicate a well-defined QTPP, which in turn leads to the development of a robust formulation and a convenient control strategy for the manufacturing process that guarantees the drug product performance. In addition, the QTPP for a new drug application (NDA) is under processing and development while it is well established for Abbreviated New Drug Application (ANDA) based on the characteristics of the Drug Substance (DS), Reference Listed Drug (RLD) label and characterization, and intended patient population. Therefore, the developed drug product from a brand or reference product is expected to have the same QTPP as that reference product (Leuenberger & Rohera, 1986; Aksu & Mesut, 2015).

**CQA, CPP, and CMA.** After QTPP identification and evaluation, the next step in the development of a drug product is the identification of the critical quality attributes (CQAs). Those CQAs are defined as "physical, chemical, biological or microbiological properties, features, or characteristics of an output material involving an accomplished drug product that must be within an appropriate limit, range, or distribution to ensure the desired product quality" (Guideline, I. H. T., 2011).

Identity, assay, degradation products, content uniformity, drug release or dissolution, residual solvents, microbial limits, moisture content, and physical attributes such as odour, size, shape, colour, friability, and score configuration are all could be considered as quality attributes which have the possibility to be either critical or non-critical (Aksu & Mesut, 2015). The harshness of harm to the patient when a certain attribute falls out of its acceptance range is the base that determines the criticality of this attribute. The criticality of an attribute can't be affected by controllability, probability of occurrence, or detectability. Input operating parameters (like speed and flow rate) or process state variables (like temperature and pressure) of a unit operation or process step are called process parameters. The criticality of a process parameter appears when its variability affects the critical quality attribute.

As a result, it must be monitored and regulated to ensure that the process outcomes are of the desired quality. Using this definition, the state of a certain process is determined by its CPPs and the CMAs of the input materials (Awotwe-Otoo, et al., 2012; Aksu & Mesut, 2015). (

Table 4) lists the typical manufacturing unit operations, material attributes, process parameters, and quality attributes for oral tablet dosage forms.

Table 4.

*Typical Input Material Attributes, Process Parameters, and Quality Attributes of tabletting Pharmaceutical Unit Operations (Lawrence, et al., 2014)*

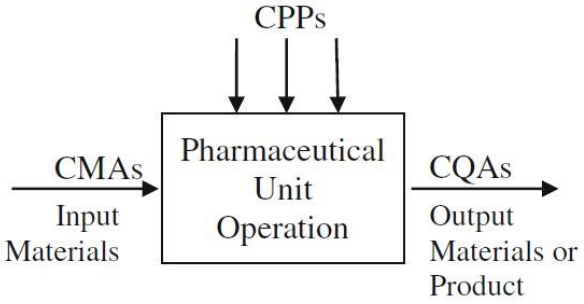
| **Input material attributes** | **Process parameters** | **Quality attributes** |
|---|---|---|
| • Particle/granule size and distribution<br>• Fines/oversize<br>• Particle/granule shape<br>• Cohesive/adhesive properties<br>• Electrostatic properties<br>• Hardness/plasticity<br>• Bulk/tapped/true density<br>• Viscoelasticity<br>• Brittleness<br>• Elasticity<br>• Solid form/polymorph<br>• Moisture | • Type of press (model, geometry, number of stations)<br>• Hopper design, height, angle, vibration<br>• Feeder mechanism (gravity/forced feed, the shape of wheels, the direction of rotation, number of bars)<br>• Feed frame type and speed<br>• Feeder fill depth<br>• Tooling design (e.g., dimension, score configuration, quality of the metal)<br>• Maximum punch load<br>• Press speed/dwell time<br>• Precompression force<br>• Main compression force | • Tablet appearance<br>• Tablet weight<br>• Weight uniformity<br>• Content uniformity<br>• Hardness/tablet breaking force/ tensile strength<br>• Thickness/dimensions<br>• Tablet porosity/density/solid fraction<br>• Friability<br>• Tablet defects<br>• Moisture content<br>• Disintegration<br>• Dissolution |

| | | |
|---|---|---|
| | • Punch penetration depth<br>• Ejection force<br>• Dwell Time | |

The capability of a process to deliver an acceptable drug product and performance, along with tolerating the variability in the process and material inputs, are called process robustness (Glodek, et al., 2006). In process robustness studies, an investigation of the effects of the variations in process parameters and material attributes is done. The CPPs that could affect drug product quality can be identified by the analysis of these experiments. Also, the analysis establishes limits or a particular range or distribution for these CPPs and CMAs, where the quality of the final drug product is guaranteed. The relationship between input CMA sand CPPs and output CQAs is shown in (Figure 7. *(Lawrence, et al., 2014)*

Figure 7

*Link input critical material attributes (CMAs) and critical process parameters (CPPs) to output critical quality attributes (CQAs) for a unit operation*




There are numerous steps to establishing process understanding that are quite similar to those for establishing product understanding. These are the steps to take: First, all known process parameters that might impact the process's performance must be identified. Then, using scientific knowledge and risk assessment, identify potentially high-risk parameters, and create specified limits or ranges for these high-risk parameters. Following that, using DoE in designing and conducting experiments when appropriate, and analysing the data from the conducted experiments, as well as determining scalability and applying first principle models to determine whether the experiment is critical or not,

in addition to linking CMAs and CPPs to CQAs. Finally, a control plan is developed, specifying the permissible ranges for critical parameters. It should be noted that when more than one material attribute or process parameter is involved, these established acceptable ranges are referred to as process design space (Aksu & Mesut, 2015).

Critical material attributes (CMAs) may belong to drug substances, in-process materials, and excipients. CMAs are defined as "physical, chemical, biological or microbiological properties, features, or characteristics of an input material that must be within an appropriate limit, range, or distribution to ensure the desired drug substance, in-process material, or excipient quality". CMAs are known to be different from CQAs in that they are for input materials that involve excipients and drug substance while the CQAs are for the output materials that includes final drug product and products intermediates. For a downstream manufacturing step, the CQA of a particular intermediate may become a CMA of the same particular intermediate (Guideline, I. H. T., 2011).

The investigation of all the identified material attributes during the formulation optimization is considered to be nearly impossible or unrealistic because there are so many attributes of the drug substance and excipients that could possibly affect the CQAs of the final drug product and also the drug intermediates. Because of this reason, a mechanism of prioritizing the material attributes and picking those permit a further study by using risk assessment is of high importance. The formulator's expertise and the common scientific knowledge should be influenced by this assessment. A material attribute is considered to be critical when a alteration in this material attribute causes a potential effect on the quality of the final product (Aksu & Mesut, 2015).

The ability to link input CMAs to output CQAs are included in product understanding which is accomplished by following these steps:

To begin, identify all known input material attributes that may have an impact on the drug product's performance. Second, using scientific knowledge and risk assessment, identify potentially high-risk attributes. Finally, these high-risk parameters must be given specific limitations or ranges. Fourth, where appropriate, use DoE in the design and execution of experiments. Fifth, analysing the data from the experiments and using first-principles models to evaluate whether or not the attribute is critical. Finally, define the acceptable ranges for critical material attributes as part of a control plan. These established

acceptable ranges are referred to as process design space when more than one excipient is involved. (Nadpara, et al., 2012).

**Risk assessment.** Risk assessment is considered to be an important start-up point for creating a design space study and continue in developing a drug product. Risk assessment in the pharmaceutical industry and development is used for prioritizing the quality attributes and the process parameters in a way that the QTPP can be achieved (Guzelturk, et al., 2015). During the initial steps of drug product development, literature and previous knowledge could serve as a base for the designing process because there is no sufficient product and process understanding of the developing drug product.

After that, more and better process and product understanding is gained, and the actual risks become more clear (ICH Q9). Beginning with the high-risk critical quality attributes and high-risk critical process parameters, risk assessment is able to find areas where the risks included in the process are in the acceptable range and also can figure out areas in which efforts to decrease or control the risks are required (Aksu & Mesut, 2015). This process chiefs to a better understanding of the developmental process, and an appropriate control strategy could be applied to guarantee that the CQAs are within the desired range and a design space study shall begin (Jain, 2104).

**Design of Experiments (DoE).** DoE is the highly systematic branch of QbD that illustrates the connection between the independent variables CPPs and the dependent variables CQAs to reach the optimal process characteristics and drug product quality (Aksu & Mesut, 2015; Series, 2011). Systematic variations of the CPPs and their simultaneous effects on the CQAs allows DoE to provide the maximum possible amount of information with the minimum amount of experiments (Gavan, et al., 2017).

The recent developments and advances in computer sciences and mathematics that aid to complex data analysis using Design of experiments (DoE), modelling with optimization and creating a design space study, and consequently, several software programs (such as MODDE, Minitab, JMP, and Design-Expert) created on mathematical models have been created to help for better formulation-process parameters relationship

understanding, thus, insurance of a high-quality product and saving time and money (Lawrence, 2008).

MODDE from MKS Umetrics is a DoE program that allows developers to complete all three major DoE stages that are required during the development of a drug product. The stages are as follows: screening (identifying the most critical factors and their ranges), optimization (finding an optimum factor combination that may be used as a set-point in the future), and robustness testing (investigation of the effects of the changes in the important factors on the set-point). The most recent versions of MODDE (9 and above) are accompanied with a new method to Design Space Estimation (DSE) and validation, taking a quantum leap toward fulfilling the Quality by Design (QbD) paradigm's objective. The DSE may be used in drug product development for robustness testing and validation. It can also forecast the greatest potential design space and evaluate the likelihood or quality of future outcomes in a safe region of operability.

Minitab statistical software is available. A wide range of design models, such as D-optimal, robust designs, two-level factorials, and others, that allow the drug product developer to check for reagent interactions and ensure that the entire parameter space is covered, as well as assist in selecting the best matrix of experimental conditions with the fewest number of experiments and the highest accuracy in predictions and estimates (Comley, 2010).

SAS JMP software offers a unified, one state that enables the drug product developer to build unique designs that are specific to his circumstance, as well as the capacity to analyze these designs. JMP's computer-generated designs enable the drug product developer to take specific account of restrictions in his factors, integrate mixing and process factors in the same design, and properly manage the difficult and extremely difficult to alter factors needed when randomization is limited (Comley, 2010).

Design-Expert software can generate test matrices for up to 50 factors. The handy power calculator is integrated into the software's design-building wizard, which is a valuable tool for generating the necessary test runs. The analysis of the graphical effects reveals the effects that stand out. The design expert then uses ANOVA to determine statistical significance. A wide range of graphical diagnostics show anomalies and outliers. Based on the validated prediction models, a numerical optimizer identifies the

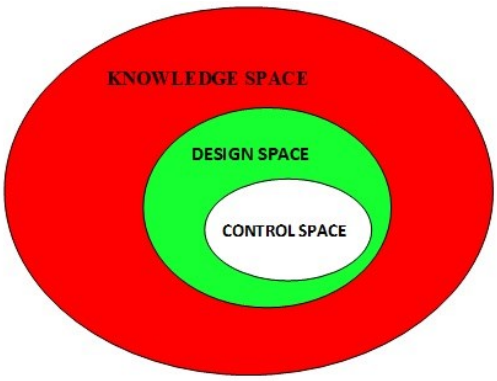
most desired factor combination. Then a sweet spot plot is shown, indicating where all of the criteria may be met. This, as advocated by the FDA, defines the design space for those related to QbD (Comley, 2010).

**Design space.** According to ICH Q8, the design space is defined 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". In other words, it defines as "the multi-variable functional relations between the CQA and the CPP and including their relations to unit operations which are found by using the literature and previous information, applying risk assessment, design of experiments (DoE) and modelling" (García-Valcárcel, 2008).

It is considered to be a study that demonstrates the relationship between CQAs and CPPs (Short, et al., 2010). it also specific for a single developmental process or a unit operation, knowing that it defines what is known to be affecting the product quality from the operational process parameters (such as compaction force). The design space is a way to show how far the understanding of a process has reached and help in developing a better product quality. (Figure 8) shows a general demonstration of the design space.

Figure 8

*General Demonstration Of The Design Space components*




**Control strategy.** The knowledge acquired by appropriately designed developmental studies ends-up with the creation of a control strategy that guarantees that the process will be preserved within the ranges demonstrated by the design space. The

control strategy is defined as a "set of planned controls derived from current product and process information that secures the process performance and product quality." (ICH Q10).

The control strategy may include the following:

- Product particularizations and specifications.
- verifying multivariate prediction models by A monitoring program (e.g., full product testing at regular intervals).
- The Control of input material attributes (e.g., drug substance, excipient, in-process material, and primary packaging material) according to a sufficient understanding of their effects on the process or product quality.
- In-process or real-time release testing instead of end-product testing (e.g., measurement and control of CQAs during processing).
- Controls for unit operations that have an effect on downstream processing or product quality (e.g., the impact of drying on degradation and particle size distribution of the granulate on dissolution) (Lawrence, et al., 2014; Aksu & Mesut, 2015).

Controls included in the control strategy include facility and equipment operating conditions, parameters and attributes associated with drug substance and drug product materials and components, in-process controls, and finished specifications, as well as associated methods and frequency of monitoring and control. It must be present, regardless of how it was created (minimal or advanced approach).

Inline controls usually are included in the control strategy in products established depending on the QbD approach (Kimbrel, 2011). The control strategy is neatly linked to criticality and design. In the QbD approach, more understanding of process and product are of high importance to create a proper control strategy. Controlling the formulation and manufacturing variables that are highly effective on the end product quality are required in order to assure pharmaceutical quality.

To ensure that all the requirements of the product quality are fulfilled, the development of a risk-based control strategy is of great importance. The QTPP is the start-up line of developing a control strategy. Characterization of the active ingredient and the important physical, chemical, biological and microbiological attributes of the formulation is the goal of the first studies. Defining the process development is also done in this stage.

There are three levels of controls that could be included in the control strategy (Lawrence, et al., 2014):

Monitoring the CQAs of the output materials in real-time by the utilization of the automatic engineering control occurs in level 1, which is considered to be the most adaptive. In a way to assure that CQAs reaches and meet the desired criteria, the process parameters are automatically adjusted, and the input material attributes are monitored. In comparison with the traditional end-product testing, real-time release testing can provide higher levels of quality assurance and could be enabled by level 1 control. It is worth mentioning that real-time release implementation is not done only by the adoption of process analytical technology (PAT).

Level 2 includes pharmaceutical control with a reduction of end-product testing and flexible process parameters and material attributes within the previously created design space. Process and product understanding is promoted by QbD along with the facilitation of variability sources identification which affects the product quality. A chance of shifting the control upstream and reduce the reliance on end-product testing is provided by understanding the multiple impacts of variability on downstream processing, drug product quality, and in-process materials (US Food and Drug Administration, 2018).

Traditionally, level 3 of control is used in the pharmaceutical industry. Extensive end-product testing and strongly restricted material attributes and process parameters are the bases of this control strategy. Any significant change in the CMAs and the CPPs need a regulatory oversight due to insufficient understanding of their effects on the CQAs and also the limited characterization of the resources of variability. The need for extra controls, acceptable variability, and the creation of acceptance criteria are issues that are still discussed and debated. In fact, levels 1 and 2 can be combined and used in a hybrid approach (US Food and Drug Administration, 2018).

## Related research

### *Compaction simulator & compaction behaviour of Paracetamol*

Compaction simulators have been invented to provide an advanced tablet press technique and take a step forward in pharmaceutical drug development. The previous techniques had some limitations in the drug material available, while formulation design

and process development takes place. Furthermore, the previous drug development mechanisms and techniques require a large amount of powder and extra time to ensure the quality of the final drug product. These facts lead the developers to invent a new technique that saves money, time and needs less effort along with producing a higher quality final product. This technique was facilitated by the compaction simulator invention.

Çelik and Marshall (1989) the building blocks, as well as the key operational features of the compaction simulator system, are shown in a research on the use of a compaction simulator system in tabletting. On eight model materials, single-ended and double-ended compression waveforms were applied. They chose 30 and 150 rpm for the tablet machine, as well as 80 and 400 MPa for the pressure. The machine's data revealed a link between the tablets' tensile strength and the average amount of electricity used throughout the process. Furthermore, the data showed poor compliance with the walker equation, as well as non-linearity plots by Heckel. (Çelik & Marshall, 1989)

Šimek et al. (2017) used a modified crystallization process to create spherical, irregular, and plate particles of paracetamol powder in order to improve Paracetamol compressibility instead of using a large amount of excipient with the normal Paracetamol powder knowing that Paracetamol has a poor flowability and compression without excipient addition. Furthermore, several sizes of each shape were prepared for the sake of expanding the screening. Then, flowability and compression ability mainly, and other material properties were analysed. They concluded that although there was a very small effect of particle size modification on material behaviour, the spherical shape of the modified particles exhibited an excellent compression behaviour which can be compressed without excipient addition (Šimek, et al., 2017).

Guang and Hua (1995) investigated three types of Paracetamol powders, which differ in their crystal shape and the manufacturers who produced the powders. They measured each powder’s crystal shape, crystal lattice, and also shape coefficient. The results were demonstrating an increase in capping and lamination when using the needle-shaped compared to the other crystals. They explained the reason for this result by

referring the cause to the typical Mohr body compression behaviour that the needle-shaped crystals have (Hong-guang & Ru-hua, 1995).

Apeji and Olowosulu (2019) examine the effects of glidants on the tabletting properties and compaction behaviour of Paracetamol granules prepared by wet granulation. The addition of glidants extra-granularly was performed on three Paracetamol formulations. Talc was added to one formulation, colloidal silicon dioxide (CSD) was added to the second, and a combination of both talc and CSD with a ratio of 1:1. Characterization of the granules was done according to the measurement of their particle size, bulk and tapped densities, angle of repose, and moisture content. Heckel, Kawakita, Walker and Compressibility-Tabletability-Compactibility (CTC) models were used in the compaction studies. Based on USP requirements, granules of each formulation are compacted to form tablets. Granule properties appeared to be similar for all the formulations irrespective of which glidant used after granule analysis was done. A higher degree of plasticity and compressibility in talc-containing granules compared to the rest of the formulations was observed in compaction studies. However, a better compact-ability and tablet-ability, which resulted in relatively better tablets, was observed with granules containing CSD and also with granules containing both glidants (Apeji & Olowosulu, 2019).

Özalp et al. (2020) employed the compaction simulator to conduct a research to investigate the compaction behaviour of weakly compressible Paracetamol powder, which was prepared by utilizing dry granulation (slugging) process with various formulation compositions. To see how various lactose-based fillers, such as Flowlac®100, Granulac®70, and the binder Kollidon® K90, affected the compressibility of the paracetamol tablet, a total of four formulations were prepared. For the formulations, the paracetamol to filler ratio was established at 1:1 and 0.8:1. To make tablets, a single punch (11.28 mm) compaction simulator was used at six different pressures (152, 210, 263, 316, 400, 452 MPa). On the manufactured tablets, control tests (hardness, thickness, and weight) were performed and compared. The findings revealed that the Granulac®70-containing formulation had a greater tensile strength than the Flowlac®100-containing

formulation, despite the fact that neither had a binder added to them. The findings also revealed that adding a binder to the paracetamol powder improves its compressibility. The conclusion shows that a low-pressure formulation containing Flowlac®100 may be used to effectively increase the compressibility of paracetamol (Ozalp, et al., 2020).

***Quality by design:***

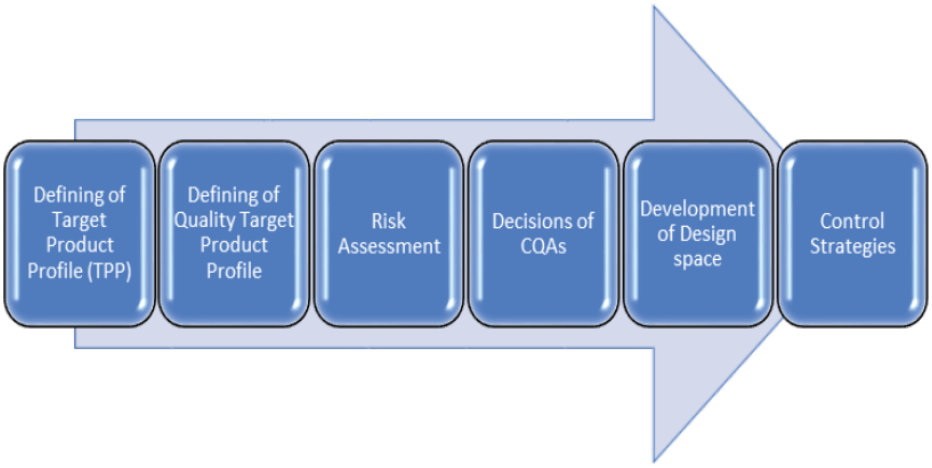
Gavan et al. (2017) applied the QbD method in the creation of sustained-release quetiapine tablets to be taken once a day. The QTPP was developed based on the kinetic release of the innovator product (Seroquel XR 200mg) and its pharmacological characteristics. The critical formulation factors for the D-optimal experimental design that were selected are the amount and ratio of matrix-forming agents and the kind of extragranular diluent. The critical quality attributes (CQAs) studied were the cumulative percentages of quetiapine released after specific time periods. Optimal formulations and design space were established following the experimental design analysis. Zero-order release kinetics and a resemblance to the innovator product in dissolution profile were shown by optimal formulations. In conclusion, the research demonstrated that the rapid creation of sustained-release tablets with comparable dissolving behaviour as the innovator product was aided by the ObD method (Gavan A. , et al., 2017).

Güncan, et al. (2017) employed the QbD method in creating alfuzosin hydrochloride ODT in order to identify connections between input attributes and outcomes. She identified several parameters in the formulation and manufacturing processes and established critical process parameters and critical material attributes using risk process techniques. Following that, several oral disintegrating tablet formulations were prepared and tested by varying the use of co-formulated disintegrating excipients and other disintegrants in combination with sodium starch glycolate and mannitol Powder flow properties were investigated. In the compression of Suitable formulations, the direct compression technique was utilized at two distinct pressure levels. These compressed tablets were tested to physical and chemical testing. The acquired results were assessed using the ANN and GEP modules (Güncan, et al., 2017).

Aksu and Mesut (2015) made a complete study about the QbD approach, its steps, advantages, disadvantages, and how the QbD will take the pharmaceutical industry a step further in developing and manufacturing the drugs with the best quality and minimum time and money costs. They explained how the QbD approach was enrolled in the pharmaceutical industry after the approval of the ICH Q8 in 2005. They also explained that the QbD approach consists of several steps that should be gone through one by one, along with designing the quality of the end product instead of testing it at the end of the manufacturing process (Aksu & Mesut, 2015). The steps of the QbD approach are detailed in the article and briefly concluded in (Figure 9).

Figure 9

*The steps of the QbD approach (Aksu & Mesut, 2015)*



# CHAPTER III

# Methodology

## Material

In this study, we used two types (code) DC Paracetamol powder. 3 batches from code APC230 PGS and 3 batches from code APC230 PGS-A. Both types were gifted from (Atabay Fine Chemicals, Turkey). Both of them contain 90% of paracetamol and 10% excipients and were prepared by using the wet granulation for DC grade. The main difference between two of them is the mesh size. They were used in the final sieving of dry powder to specify a particular granular size, a mesh size of 18 (1.00 mm) has been used in type 1, and 12 Mesh size (1.68 mm) was used regarding type 2 sieving as shown in (Table 5).

Table 5.

*Types of Paracetamol Powder and Their Batches, Mesh Size and composition*

| Type | DC Paracetamol (Code) | Batch Number | Sieve Size (Mesh) | % of Paracetamol | % of Excipients |
|---|---|---|---|---|---|
| **Type 1 (A)** | APC230 PGS | 26 | 18 | 90% | 10% |
| | | 27 | 18 | 90% | 10% |
| | | 28 | 18 | 90% | 10% |
| **Type 2 (B)** | APC230 PGS-A | 29 | 12 | 90% | 10% |
| | | 30 | 12 | 90% | 10% |
| | | 31 | 12 | 90% | 10% |

The letter A resembles Type 1 and the letter B resembles Type 2. Each type study was coded as the (Table 6) is showing.

Table 6.

*The Batches of Each Type and Their Formulation Codes*

| Type | Batch number | Formulation Code |
|---|---|---|
| **A** | 26 | AA |
| | 27 | AB |
| | 28 | AC |
| **B** | 29 | BA |
| | 30 | BB |
| | 31 | BC |

**Equipment Used**

(Table 7) is giving a brief summary about all equipment used and the study and their purpose of usage.

Table 7.

*The equipment used in this study*

| **Purpose** | **Equipment** |
|---|---|
| Tapped density | Erweka 195 SVM 203 |
| Particles Surface Area measurement | Quantachrome Quadrosorb SI |
| Morphological studies (SEM) | Zeiss EVO/LS10 |
| Compaction studies/ Tableting | Compaction Simulator Stylcam 200R |
| Thickness and Diameter measurement | Digital Calliper (TCM) |
| Weigh measurement | AB 104-S/PH analytic balance |
| Hardness Tester | Erweka TBH 225 |
| Friability Test | Erweka TAR 220 |
| Disintegration Test | Erweka 240 ZT 322 |

## Powder Characterization

### *Powder Densities*

Two different types of DC Paracetamol powder had the following tested.

**Bulk density**. 100g of each batch was put into a 100 ml tarred graduating cylinder. The powder stuck to the cylinder's wall was retrieved by gently tapping it twice. After reading the volume directly from the cylinder, the bulk density was estimated using the mass/volume relationship. This was done in accordance with USP (USP 35, 2011).

**Tapped density.** In the measuring cylinder, 100 g of each batch were poured, and the initial volume was recorded. According to USP, the powder was mechanically tapped by SVM machine (Erweka, 195 SVM 203) as seen in (Figure 10), and volume readings were taken until little further volume change was observed (USP 35, 2011).

Figure 10

*Tapped density measurement by SVM Machine (Erweka, 195 SVM 203)*


**True density.** The true density of the batches was measured by helium pycnometer using (Quantachrome Ultrapyc 1200e). This device uses helium to determine the sample's volume by measuring the change in the pressure of the helium in a calibrated volume. Apparent particle density is derived automatically After sample weight has been specified. This was done three times, and then the mean was calculated (Viana, et al., 2002). This

was done by Yildiz Technical University, Science and Technology Application and Research Center, Turkey.

***Particles Surface Area***

The specific surface areas of each type were determined using the Brunauer–Emmett–Teller (BET) method. The primary idea here is the adsorption of gases onto solid surfaces after the formation of physical or chemical forces of interaction (Dollimore et al., 1976). In our case, nitrogen gas was used, and its adsorption was measured by an automated volumetric adsorption instrument (Quantachrome Quadrosorb SI) (Naderi, 2015). This was done by Yildiz Technical University, Science and technology application and research center, Turkey.

***Morphological studies***

The morphology of the granules of both types and their size were inspected by (Zeiss EVO/LS10) scanning Electron Microscope (SEM) imaged by Yildiz Technical University, Science and technology application and research centre, Turkey. Double-adhesive carbon tape was used to adhere a single layer of powder to the metal stubs. The powders were then expectorated with gold while under argon. Images were taken at a magnification of 250x with a 10.00kV accelerating voltage (Altamimi, et al., 2019).

***Powder Flowability***

Hausners' ratio & compressibility index (carrs' index) were calculated to obtain powder's flowability by using tapped density (*P* tapped) and bulk density (*P* bulk). The bulk and tapped densities were used to calculate the Carrs' index ($\text{Carrs' index} = \left(\frac{P\ tapped - P\ bulk}{P\ tapped}\right) \times 100$ Equation ) and the Hausners' ratio ($\text{Hausners' Ratio} = \left(\frac{P\ tapped}{P\ bulk}\right)$ Equation ) to provide a measure of the flow properties and compressibility of powders (Carr, 1965; Hausner, 1967; Shah, et al., 2008).

**Quality by Design study**

***Quality Target Product Profile***

QTPP is a start-up line of the QbD approach, which is essential in creating a foundation of the design for product development. There are several considerations in QTPP, which involves dosage form, delivery systems, administration, dosage strength container closure system, attributes affecting pharmacokinetic characteristics and therapeutic delivery or release, which are appropriate to the developing drug product dosage form, and the criteria of the drug product quality. QTPP for Paracetamol tablet (Table 8) was defined based on the characteristics of the drug substance, previous literature and US pharmacopoeia. It is worth noticing that target values must be reached in order to achieve the best design space to ensure the lowest probability of failure (Patil & Pethe, 2013; Mesut, et al., 2015).

Table 8.

*Quality Target Product Profile of Paracetamol Tablet*

| **Specification** | Quality Target Product Profile |
|---|---|
| Dosage Form | Immediate Release Tablet (Orally) |
| Pharmacological Action | Antipyretics |
| Tablet weight | $525 \leq$ weight mg $\geq 475$ |
| Weight variation | ±5% |
| Hardness | More than 50N |
| Disintegration | Less than 15 minutes in distilled water |
| Friability | < 1% |

***Risk assessment***

A risk assessment study was established (Table 9) in order to identify the CQAs through analysing the available attributes and linking them to the CPPs. Our current knowledge, along with literature and ICH Q9 risk management guidelines, were the main bases on which risk ranking determination was based. The identification of the CQAs was according to the level of CPPs impaction on the attributes. The level of impaction is referred to as very high, high, medium, very low and low, where very high, high and

medium impacted attributes were considered to be critical while very low and low impacted attributes were excluded from the study (Ristić, 2013; Heuck Jr, 2007). The CQAs were then determined as hardness, disintegration, and friability of the tablets as they are the most effective attributes on the final product quality.

Table 9.

*Risk Assessment of The Critical Process Parameters Against The Quality Attributes*

| **Critical Process Parameters** | **Quality Attributes** | | | | |
|---|---|---|---|---|---|
| | Tablet weight | Weight variation | Hardness | Disintegration | Friability |
| **Compaction Force** | Low | Low | Very High | Very High | Very High |
| **Method of excipient addition** | Very Low | Very Low | High | High | Medium |
| **Mesh Size** | Low | Low | Very High | Very High | High |

***Design of Experiment***

DoE study was made based on MODDE 12.1 statistical software (Umetrics, Sweden). A partial least squares (PLS) regression model was used in fitting and developing prediction models. Three batches from each type were used to ensure the accuracy of the results (Rosipal, 2011). Those batches were compressed at three different forces 15, 30, and 45kN as approximated values. Compaction force, mesh size and method of excipient addition were considered as factors and hardness, friability and disintegration were considered as responses. A total of 18 experiments were generated to be assured about the final product quality. The results of these applications were used to form a controlled and well-defined design space in order to obtain a robust set point.

**Tableting**

A compaction simulator (Stylcam R200, Medelpharm, France) (Figure 11) Machine Speed: 10 rpm with Simulated machine (Fette 102i-Euro B - 28800 Tab/Hour) with an 11.28mm round, flat-faced Euro B punch was used for compacting the powder to form a tablet (Michaut, et al., 2010).

100g were taken from the powder by using (Mettler Toledo AB 104-S/PH analytic balance), and 20% of extra powder was added to account for the lost powder during the compaction procedure to produce 20 tablets that have 500mg of weight. It has to be noticed that the powder has been used without any further excipient addition.

Twenty tablets were pressed for each force (15, 30, 45 kN), and the same process was repeated for each batch. Die filling was done with automated filling. Proceeding to weigh each tablet separately by (AB 104-S/PH analytic balance, Mettler Toledo, Belgium) after compaction process took place (Ozalp, et al., 2020).

***Compaction behaviour***

Compaction behaviour data of the compacted powder consists of ejection force, compression, rearrangement, Plastic, Elastic energies, and heckle plot given by (Analis Software 2006, Medelpharm, France) which is linked to the compaction simulator. Plots were made by (GraphPad Prism 8.3.0, La Jolla, CA, USA). The values were calculated by (Analis Software 2006, Medelpharm, France)

Figure 11

*Compaction Simulator (Stylcam R200, Medelpharm, France)*

**Measurements of Quality Attributes (Quality Control Tests)**

***Weight variation***

According to USP, each batch's 20 tablets (n=20) were weighed separately and their weights were recorded. The average weight of the tablets was then determined, and the percentage deviation was calculated (USP 35, 2011).

$$\text{Deviation (\%)} = \left(\frac{\text{tablet weight} - \text{average tablet weight}}{\text{average tablet weight}}\right) \quad \text{Equation 7}$$

***Thickness and Diameter***

The thickness and diameter were measured for 20 tablets from each batch after Twenty-four hours from the compaction process by automatic calliper (0-150mm TCM), as shown in (Figure 12).

Figure 12

*Thickness and Diameter Measurements by Digital Calliper (TCM)*


***Hardness (breaking force)***

The hardness of 3 tablets (n=3) was taken from each batch, and their hardness average regarding the compaction forces was obtained 24 hours from the compaction process. According to USP Pharmacopoeia, the test was performed using hardness tester machine (TBH 225 device, Erweka, Germany), as seen in (Figure 13). The equipment is primarily made up of two jaws that face each other and typically move towards each other. In the test, each tablet was put between the jaws, and the force required to crush the tablet was measured as (N) (USP 35, 2011).

Figure 13

*Hardness Measurements by  Hardness Tester Machine(Erweka, TBH 225 device)*


***Friability***

According to USP pharmacopoeia, 13 tablets from each batch were thoroughly de-dusted before to testing and precisely weighed after 24 hours after the compaction process. The tablets were then put in the drum, which was spun 100 times (25 rpm) before the tablets were removed. Finally, remove any loose dust from the tablets as previously, and precisely weigh the tablets using a Friability tester (TAR 220, Erweka, Germany), as indicated in (Figure 14), in regards to the compaction pressures applied to the compacted powder.  (Salpekar & Augsburger, 1974; USP 35, 2011).

Figure 14

*Friability Measurements by Friability Tester Machine (Erweka, TAR 220)*

***Disintegration***

1000 mL of water was filled in a low-form beaker under a thermostatic arrangement for heating the fluid (37.00 ± 0.5 °C) and a device for raising and lowering the basket in the immersion fluid at a constant frequency rate of 29–32 cycles/min using Erweka disintegration tester (240 ZT 322, Erweka, Germany) (Figure 15). As in the hardness test, three tablets were taken from each batch after 24 hours from the compaction process regarding the compaction forces applied (USP 35, 2011).

Figure 15

*Disintegration time measurements by Disintegration Tester (Erweka, 240 ZT 322)*

**Statistical difference**

***Between Two Types***

Statistical difference between the two types has been investigated by calculating the difference between the average of type A batches (AA, AB, and AC) and the average of type B batches (BA, BB and BC) and determining whether the difference is statistically significant or not using one-way ANOVA test (single factor with confidence interval = 0.05).

### *Batch to Batch Variation Analysis*

Batch to batch variation was checked between the 3 batches of each type. Further investigation was done to determine which batch is statistically different if batch to batch variation was found. This investigation was done using one-way ANOVA test (single factor with confidence interval = 0.05) to Identify the significant difference in order to determine if there is batch to batch variation or not (Jin & Guo, 2013).

## Data Analysis

An experimental design study was performed to examine the impact of variable modifications on the critical outputs and experimental data analyzed using the MODDE Pro 12.1 statistical modelling software that enables optimization. The experimental data acquired from the direct compression technique were uploaded to MODDE, then an optimal formulation was proposed by the software. Using the Partial least squares regression (PLS) model, experimental data were fitted in a statistical module of MODDE 12.1 Pro. Also, the validity of the experimental design was checked using the analysis of variance (ANOVA) test. The statistical parameters found were R2, indicating the variation explained by the model, and Q2, the fraction of the variation of the response that can be predicted by the model, validity, and reproducibility. Additionally, the validity of the model and experimental design was verified by the ANOVA test (Aksu, et al., 2012).

A model with R2 lower than 0.5 is a model with a relatively low significance which is considered to be an overestimation of the goodness of fit. Q2 should be greater than 0.1 for a significant model; for a good model, it must be greater than 0.5, which is considered to be an underestimation of the goodness of fit. Because of Q2 underestimation of the goodness of fit, it is known to be the best and most sensitive indicator for the goodness of a model fit. The difference between R2 and Q2 should be smaller than 0.3 (Betterman, et al., 2012).

Model validity is a test of diverse model problems such as the presence of outliers, incorrect model, or transformation problems. Those problems might be statistically significant if the validity value is less than 0.25. Moreover, validity could be low or labelled as it can’t be calculated even if the model is good in case of a minimal difference and nearly identical replicates. Finally, reproducibility is the variations of the responses

under the same circumstances (pure error) compared to the total variation of the responses. Reproducibility should be greater than 0.5 in a significant model. In all the responses, reproducibility values were higher than 0.95, which is considered an indication of a low pure error and very minor total variations in the responses (Betterman, et al., 2012).

***Regression coefficient***

The signs of coefficients show the positivity or negativity of a relationship between a predictor variable and a response variable. A positive sign occurs when both the predictor and the response variable rise. A negative sign occurs when the predictor variable rises while the response variable declines.

The coefficient value assembles the mean change in the response that occurs as a result of a one-unit change in the predictor (Schielzeth, 2010).

***Sweet spot***

The sweet spot plot shows and highlights the areas where the responses (hardness, friability and disintegration) are at their specified ranges. Unlike design space, the sweet spot does not include the probability of failure. The sweet plot is segmented, and each segment is coloured by a specific colour. The green colour is the sweet spot area where all three responses are included within their range. Light blue indicates that two criteria were met within their selected ranges. Dark blue indicates that only one criterion has been met within its range (Lindberg, 2010).

**Design space**

According to ICH Q8, the design space is defined 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". In other words, it defines the "multi-variable functional relations between the CQA and the CPP and including their relations to unit operations which are found by using the literature and previous information, applying risk assessment, design of experiments (DoE) and modelling" (García-Valcárcel, 2008). The design space is a way to show how far the understanding of a process has reached and help in developing a better product quality. It is considered to be a study that demonstrates the relationship between CQAs and CPPs (Short, et al., 2010).

# CHAPTER IV

## Findings and Discussion

### Powder Characterization

Type A and Type B paracetamol DC batches were tested and averages were calculated (Table 10). Type A had lower bulk and true densities and a higher tap density compared to type B. In addition, a Mesh size of 18 was used when preparing type A, while 12 Mesh size was used with type B.

As a result of using two different sieve sizes, its effect on the surface area of the powder could be explained as the larger surface area indicates smaller particles in type A than in type B. It is evident that both of the powders consist of irregularly shaped particles with a smaller particles size for type A, as seen in (Figure 16).

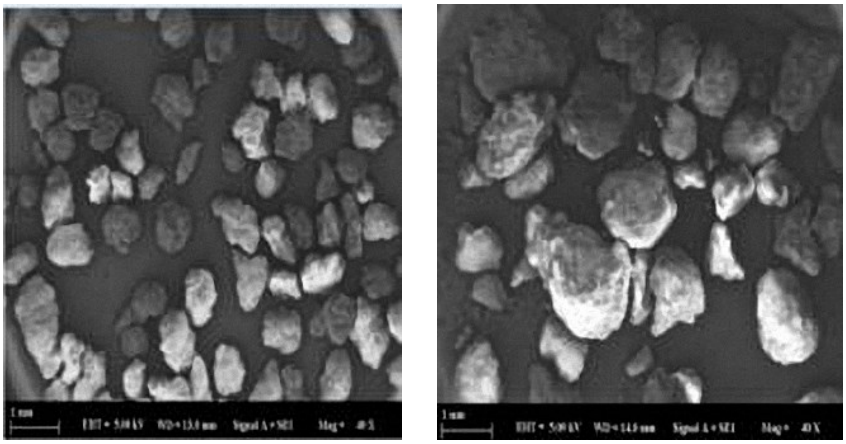
Table 10.

*Powder Properties of type A and B*

| Type | Bulk density(g/ml) | Tap Density (g/ml) | True density ($g/cm^3$) | Surface Area (m2/g) |
|---|---|---|---|---|
| **Type A** | 0.606 ± 0.0047 | 0.703 ± 0.004 | 1.304 ± 0.003 | 4.408 ±0.065 |
| **Type B** | 0.626 ± 0.0047 | 0.681 ± 0.001 | 1.305 ± 0.003 | 1.441 ± 0.043 |

Figure 16

*Morphology of Powders by Scanning Electron Microscope (SEM), Type A and Type B (250X Magnification)*



**(Type A)** **(Type B)**

**Powder Flowability.** The flowability of a powder can commonly be measured in two ways, Hausners' ratio and Carrs' index. As (Table 11) is showing, type B gained a lower Hausners' ratio that equals 1.0841, which indicates low inter-particulate friction indicating a higher flowability. Type A has a lower flowability and higher inter-particulate friction as it has a 1.1594 Hausners' ratio. Carrs' index was 13.735 in type A.

In comparison, type B has a lower value of Carrs' index, which equals 7.843 (Hausner, 1967; Grey & Beddow, 1969).

Looking back to the flowability scale shown in (

Table 1) in the general information section, the flowability of type B is considered to be Excellent (Hausners' ratio 1.00-1.11, Carrs' index ≤10) because it has lower Hausners' ratio (1.0841) and lower Carrs' index (7.843). While it is considered to be good (Hausners' ratio 1.12-1.18, Carrs' index 11-15) in type A because it has a higher Hausners' ratio than type B (1.1594) and also a higher Carrs' index (13.735). *(Taylor & Aulton, 2013)*

Table 11.

*Hausners' Ratio and Carrs' Index % Values for Type A and Type B*

| Type | Hausners' Ratio | Carrs' Index % |
|---|---|---|
| **Type A** | 1.1594 ± 0.016 | 13.735 ± 1.242 |
| **Type B** | 1.0841 ± 0.008 | 7.843 ± 0.693 |

**Compaction Results**

The following (Table 12) shows the mean compaction force used for pressing the compacted powder, the average weight, the average thickness, and the average diameter of each compacted powder with their standard deviations for 20 tablets from each batch at every compaction force applied. It is noticed that the average thickness of type A is higher than the average thickness of type B at the same compaction force. No lamination or capping was observed after compacting the batches of both types without lubricant.

Table 12.

*Applied Force (kN) results of all batches in two types powder. (Weight variation, Thickness, and Diameter),* (n=20)

| Type | Formulation Code | Compaction Force(kN) | Average Weight (mg) | Average Thickness (mm) | Average Diameter (mm) |
|---|---|---|---|---|---|
| **A** | AA | **15.21 ± 0.33** | 503.13 ± 2.00 | 4.48 ± 0.06 | 11.30 ± 0.005 |
| | AB | **15.23 ± 0.22** | 501.74 ± 1.08 | 4.45 ± 0.04 | 11.30 ± 0.005 |
| | AC | **15.16 ± 0.22** | 501.25 ± 1.44 | 4.46 ± 0.02 | 11.30 ± 0.005 |
| **B** | BA | **14.75 ± 0.56** | 501.29 ± 2.69 | 4.37± 0.04 | 11.30 ± 0.005 |
| | BB | **14.97 ± 0.66** | 501.51 ± 2.75 | 4.39 ± 0.84 | 11.30 ± 0.005 |
| | BC | **15.14 ± 0.72** | 500.73 ± 2.31 | 4.35 ± 0.08 | 11.31 ± 0.005 |
| **A** | AA | **30.23 ± 0.49** | 501.77 ± 1.31 | 4.22 ± 0.05 | 11.29 ± 0.004 |
| | AB | **30.02 ± 0.35** | 501.60 ± 1.46 | 4.23 ± 0.09 | 11.29 ± 0.005 |
| | AC | **30.11 ± 0.24** | 502.66 ± 1.26 | 4.19 ± 0.09 | 11.28 ± 0.005 |
| **B** | BA | **30.08 ± 0.75** | 498.91 ± 1.85 | 4.06 ± 0.06 | 11.29 ± 0.004 |
| | BB | **30.15 ± 0.58** | 502.80 ± 3.00 | 4.09 ± 0.69 | 11.30 ± 0.004 |
| | BC | **29.88 ± 0.78** | 499.57 ± 2.51 | 4.07 ± 0.10 | 11.29 ± 0.021 |
| **A** | AA | **45.05 ± 0.47** | 502.55 ± 1.64 | 4.13 ± 0.08 | 11.28 ± 0.004 |
| | AB | **45.05 ± 0.65** | 498.28 ± 1.73 | 4.11 ± 0.05 | 11.28 ± 0.004 |
| | AC | **45.12 ± 0.32** | 504.36 ± 1.15 | 4.15 ± 0.02 | 11.28 ± 0.004 |
| **B** | BA | **44.86 ± 0.63** | 499.20 ± 2.25 | 4.04 ± 0.31 | 11.29 ± 0.005 |
| | BB | **45.06 ± 1.43** | 503.74 ± 2.56 | 4.02 ± 0.04 | 11.29 ± 0.005 |
| | BC | **44.96 ± 0.56** | 501.52 ± 2.98 | 4.03 ± 0.18 | 11.29 ± 0.005 |

### *Compaction Behaviour*

#### Rearrangement energy

The (Table 13) is showing the elastic energy for each batch at each compaction force. There is significant difference between all the batches of type A ($P$<.001) and no significant difference between the batches of type B ($P$=.56) at 15 kN compaction force, this means that there is batch to batch variation between type A batches. At 30kN compaction force, AA is significantly different from AB ($P$<.001) and AC ($P$<.001) while AB and AC are not significantly different from each other ($P$=.64), which indicates that there is batch to batch variation. On the other hand, type B batches have no significant

difference between each other (*P*=.38). Finally, at 45kN, there was no significant difference neither between type A batches (*P*=.53) nor between type B batches (*P*=.45), batch to batch variation was absent. The existence of batch to batch variation at 15 and 30kN and its absence at 45 kN could be explained by the small particle size of type A powder that leads to increased friction and adhesion forces which in turn effected the rearrangement energy. Moreover, as the compaction force increases, the effects of friction and adhesion forces on the rearrangement energy decreases which reduces the possibility of having batch to batch variation.

Table 13.

*Rearrangement Energy (J) for Each Batch of Each Type at All Compaction*

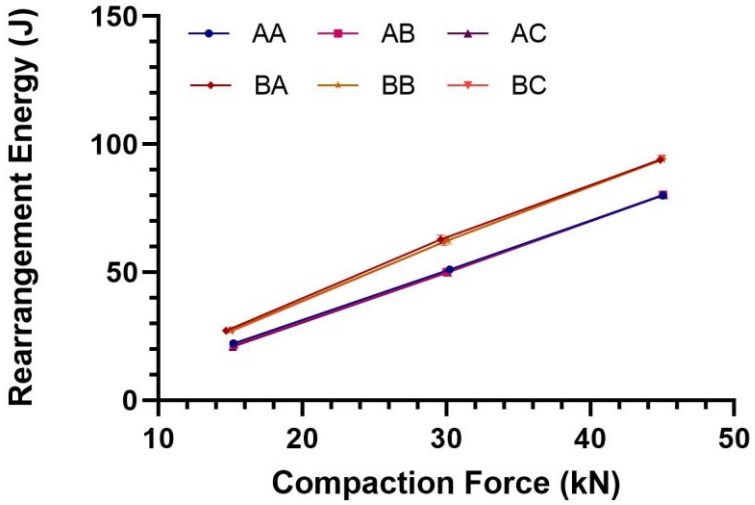
| **Compaction Force (kN)** | **Type** | **Formulation Code** | **Rearrangement Energy (J)** |
|---|---|---|---|
| **15±0.25** | **A** | AA | 22.201 ± 0.527 |
| | | AB | 21.656 ± 0.249 |
| | | AC | 20.937 ± 0.306 |
| | **B** | BA | 27.157±1.301 |
| | | BB | 27.142 ± 1.275 |
| | | BC | 27.24 2 ± 1.075 |
| **30±0.23** | **A** | AA | 51.034 ± 0.824 |
| | | AB | 50.099 ± 0.524 |
| | | AC | 49.996 ± 0.306 |
| | **B** | BA | 62.055 ± 1.792 |
| | | BB | 62.521 ± 1.574 |
| | | BC | 61.988 ± 1.574 |
| **45±0.14** | **A** | AA | 80.116 ± 0.618 |
| | | AB | 80.347 ± 1.152 |
| | | AC | 80.230 ± 0.306 |
| | **B** | BA | 93.895 ± 1.267 |
| | | BB | 94.04 5± 1.267 |
| | | BC | 94.340 ± 1.067 |

It has been noticed that type A (AA, AB, and BC), which has a small particle size, consumed less energy in the rearrangement stage comparing to type B (BA, BB and BC)

at all compaction forces applied, which required more considerable rearrangement energy amount (Figure 17). These results were not expected because type B had lower inter-particulate friction than type A, which means that type B should consume less rearrangement energy than type A (Roberts & Rowe, 1987; Çelik, et al., 1996). This result is probably due to the formulation composition differences between Type A and type B or due to the different methods of excipient addition used during wet granulation processing.

Figure 17

*Rearrangement Energy (J) Against Compaction Force (Kn) for Type A Batches and Type B Batches (n=20)*




**Elastic energy**

The (Table 14) is showing the elastic energy for each batch at each compaction force. There is no significant difference between AA and AB ($P$=.62) while the is significant difference between AA and AC ($P$=.002), and between AB and AC ($P$<.001) batches of type A while no significant difference is observed between the batches of type B ($P$=.29) at 15 kN compaction force, this means that there is batch to batch variation between type A batches. At 30kN compaction force, AB is significantly different from AA ($P$=.04) and AC ($P$=.01) while AA and AC are not significantly different from each other ($P$=.75), which indicates that there is batch to batch variation. On the other hand,

type B batches have no significant difference (*P*=.12) between each other. Finally, at 45kN, there was no significant difference neither between type A batches (*P*=.44) nor between type B batches (*P*=.42), batch to batch variation was absent. This result could be explained by the increased amount of small particles of type A in 500mg volume that increased the probability of batch to batch variation in the elastic energy. This phenomenon is reduced as the compaction force increases.

Table 14.

*Elastic Energy (J) for Each Batch of Each Type at All Compaction*

| Compaction Force (kN) | Type | Formulation Code | Elastic Energy(J) |
|---|---|---|---|
| **15 ± 0.25** | **A** | AA | -0.400 ± 0.024 |
| | | AB | -0.397 ± 0.018 |
| | | AC | -0.420 ± 0.016 |
| | **B** | BA | -0.371 ± 0.023 |
| | | BB | -0.361 ± 0.034 |
| | | BC | -0.353 ± 0.035 |
| **30 ± 0.23** | **A** | AA | -1.234 ± 0.063 |
| | | AB | -1.197 ± 0.038 |
| | | AC | -1.229 ± 0.027 |
| | **B** | BA | -1.065 ± 0.032 |
| | | BB | -1.044 ± 0.048 |
| | | BC | -1.054±0.052 |
| **45 ± 0.14** | **A** | AA | -3.078 ± 0.086 |
| | | AB | -3.124 ± 0.007 |
| | | AC | -3.067 ± 0.064 |
| | **B** | BA | -2.675 ± 0.018 |
| | | BB | -2.655 ± 0.018 |
| | | BC | -2.580 ± 0.051 |

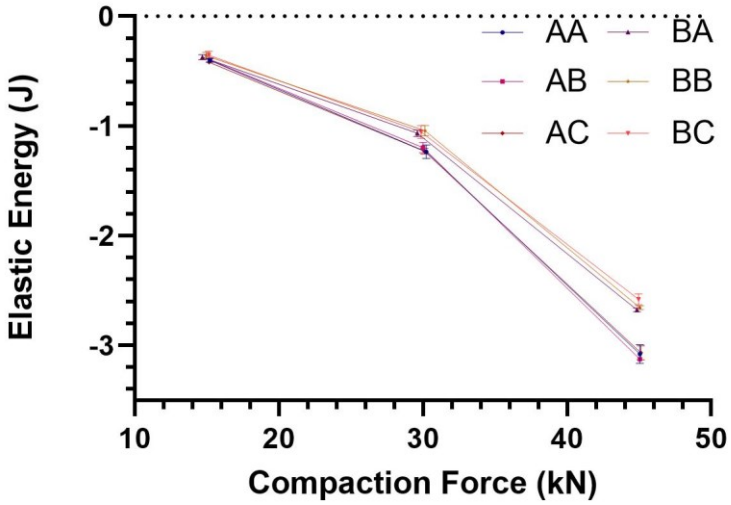
Elastic energy is negatively marked because it is lost energy. As shown in (Figure 18), the elastic energy was increasing along with the increasing compaction force.

Type A which has small particle size has higher elastic energy than type B which has larger particle size when all compaction forces (15, 30 and 45kN) were applied.

Looking at (Figure 18 *Elastic Energy (J) Against Compaction Force (kN) Type A Batches and Type B Batches (n=20).*, it is obvious that the difference between type A and type B elastic energies is increasing as the compaction force increases.

Figure 18

*Elastic Energy (J) Against Compaction Force (kN) Type A Batches and Type B Batches (n=20).*




**Plastic energy**

The (Table 15) is demonstrating the plastic energy for each batch at each compaction force. There was no significant difference between type A batches at 15kN (*P*=.33), at 30kN (*P* =.56), and at 45kN (*P* =.13). Moreover, also no significant difference observed between type B batches at 15kN (*P*=.63), at 30kN (*P* =.83), and at 45kN (*P* =.82) compaction forces applied.

Table 15.

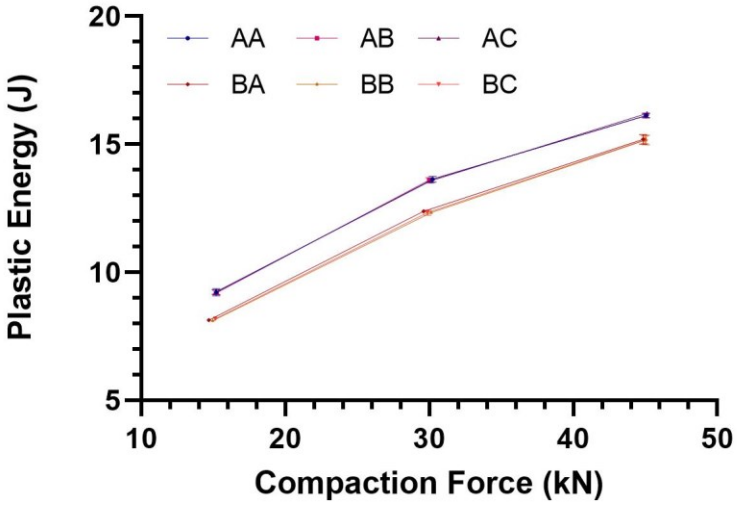
*Plastic Energy (J) for Each Batch of Each Type at All Compaction Forces*

| Compaction Force (kN) | Type | Formulation Code | Plastic Energy (J) |
|---|---|---|---|
| **15 ± 0.25** | **A** | AA | 9.215 ± 0.147 |
| | | AB | 9.195 ± 0.071 |
| | | AC | 9.227 ± 0.09 |
| | **B** | BA | 8.127 ± 0.058 |
| | | BB | 8.107 ± 0.045 |
| | | BC | 8.187 ± 0.038 |
| **30 ± 0.23** | **A** | AA | 13.629 ± 0.117 |
| | | AB | 13.608 ± 0.085 |
| | | AC | 13.570 ± 0.078 |
| | **B** | BA | 12.379 ± 0.008 |
| | | BB | 12.335 ± 0.016 |
| | | BC | 12.329 ± 0.096 |
| **45 ± 0.14** | **A** | AA | 16.124 ± 0.079 |
| | | AB | 16.119 ± 0.105 |
| | | AC | 16.212 ± 0.074 |
| | **B** | BA | 15.19 9± 0.194 |
| | | BB | 15.174 ± 0.198 |
| | | BC | 15.167 ± 0.154 |

In (Figure 19), type A which has smaller particle size has higher plastic energy than type B which has larger particle size. It has been noticed that when the compaction force was increasing from 15kN to 45kN, the plastic energy for both types were also increasing ($P$<.001).

Figure 19

*Plastic Energy (J) Against Compaction Force (kN) for Type A Batches and Type B Batches (n=20)*



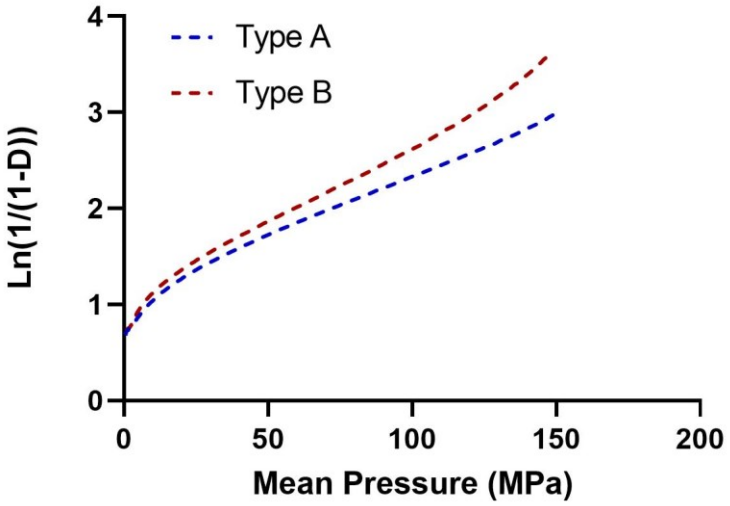

**Heckel Plot**

Heckel plot taken at 15 kN compaction force (Figure 20) with an average mean yield pressure (*Py*) of type A and type B is (83.70±0.8) and (64.30±0.5), respectively. It is demonstrated that type B has more plastic deformation and larger densification. In contrast, type A presented with less plastic deformation and smaller densification. This can be explained by the degree of the surface area of each type. Type B had the smallest surface area meaning that it contains larger particles, leading to increased susceptibility to deformation and more densified powder particles. Type A, on the other hand, had the largest surface area indicating a smaller particle size resulting in decreased susceptibility to deformation and less densification of powder particles (Roberts & Rowe, 1986)

It is worth mentioning that the lower *Py* value that type B has, the more indication of an improvement in the compressibility (Geoffroy & Carstensen, 1991) in addition to lower plastic energy, as illustrated in (Figure 19) (Patel, et al., 2007).

Figure 20

*Heckel Plot for type A and type B at 150MPa Mean pressure*

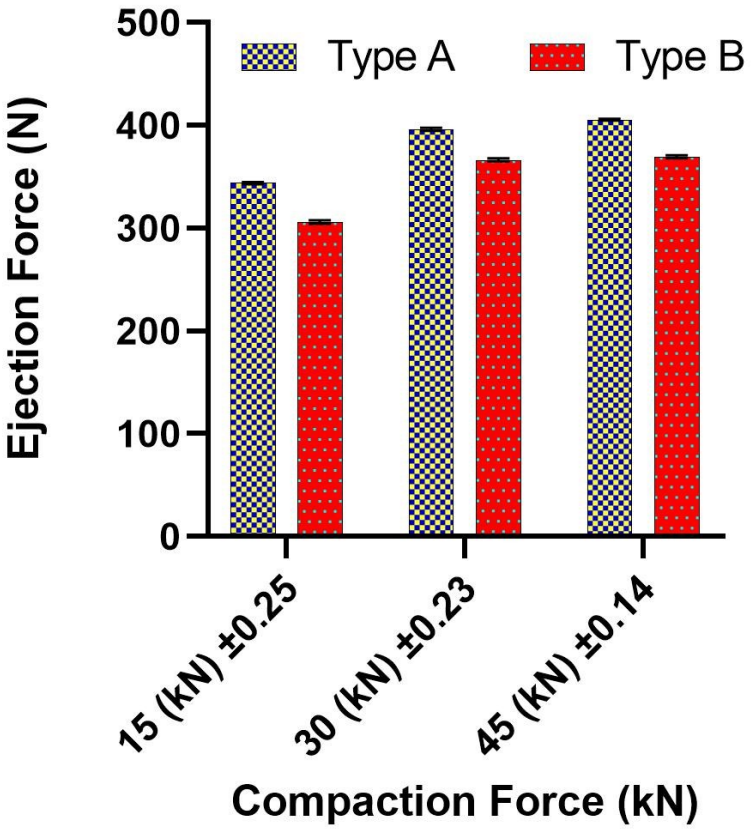



**Ejection Force of Tablet**

Since type A has the larger surface area between the two types, as mentioned in (Table 10), it is prone to more friction between particles and die wall, which in turn increases the requirement of ejection force, suggesting a positive correlation between surface area and ejection force (Rojas & Kumar, 2011). As demonstrated in (Figure 21), type A had a higher ejection force than type B at all compaction forces that have been applied on the powders (15, 30 and 45 kN), and the differences were statistically significant ($P$<.001) at all compaction forces applied) as it was calculated by comparing the averages of the batches of each type.

Figure 21

*The Relation Between Ejection Force (N) and Compaction Force (kN) for The Average of Type A Batches and Type B Batches (n=60)*



## Quality Control Tests

Table 16.

*Quality control tests were done and average values were calculated with their standard deviations Max Weight Variation (%) n=20, Hardness (N) n=3, Friability (%) n=13, and Disintegration time (min.) n=3*

| Compaction Force (kN) | Type | Formulation Code | Max(%) Wt.variation | Hardness (N) | Friability (%) | Disintegration (min.) |
|---|---|---|---|---|---|---|
| **15±0.25** | **A** | AA | 0.63 ± 0.39 | 129.00 ± 2.16 | 0.957 | 4.527 ± 0.09 |
| | | AB | 0.41 ± 0.21 | 129.16 ± 0.62 | 0.974 | 4.423 ± 0.02 |
| | | AC | 0.90 ± 0.28 | 130.01 ± 0.36 | 0.960 | 4.367 ± 0.05 |
| | **B** | BA | 1.17 ± 0.53 | 138.00 ± 1.45 | 0.876 | 7.483 ± 0.24 |
| | | BB | 1.39 ± 0.54 | 139.66 ± 1.24 | 0.881 | 7.540 ± 0.02 |
| | | BC | 0.81 ± 0.46 | 139.00 ± 1.63 | 0.849 | 7.390 ± 0.14 |
| **30±0.23** | **A** | AA | 0.74 ± 0.26 | 198.66 ± 2.62 | 0.722 | 16.470 ± 0.38 |
| | | AB | 0.76 ± 0.29 | 197.33 ± 1.70 | 0.718 | 16.687 ± 0.10 |
| | | AC | 0.44 ± 0.25 | 200.66 ± 1.88 | 0.723 | 16.810 ± 0.15 |
| | **B** | BA | 0.98 ± 0.37 | 205.00 ± 2.16 | 0.630 | 20.783 ± 0.40 |
| | | BB | 1.34 ± 0.59 | 206.00 ± 2.27 | 0.624 | 20.623 ± 0.37 |
| | | BC | 1.04 ± 0.50 | 203.00 ± 2.16 | 0.627 | 20.307 ± 0.07 |
| **45±0.14** | **A** | AA | 0.67 ± 0.32 | 230.00 ± 2.44 | 0.612 | 24.167 ± 0.47 |
| | | AB | 0.73 ± 0.34 | 231.33 ± 2.47 | 0.633 | 24.850 ± 0.04 |
| | | AC | 0.71 ± 0.22 | 229.00 ± 2.62 | 0.624 | 24.553 ± 0.11 |
| | **B** | BA | 1.22 ± 0.45 | 238.33 ± 3.43 | 0.551 | 27.917 ± 0.35 |
| | | BB | 0.88 ± 0.50 | 237.00 ± 3.26 | 0.546 | 27.367 ± 0.55 |
| | | BC | 1.08 ± 0.59 | 239.00 ± 2.40 | 0.557 | 27.367 ± 0.41 |

It is obvious in (Table 16), it is noticed that increasing compaction force positively effects hardness and disintegration, unlike friability which is negatively affected by increasing compaction force.

***Weight variation***

It is noticed in (Table 16) that the average weight and the max weight variation are both compatible with the QTPP principles of the Paracetamol tablet as it should not exceed 5%.

***Tablet Friability***

It is illustrated in (Table 16) that the friability levels for type A and type B at different compaction forces. It is noticeable that as long as the compaction force is increasing, friability is decreasing. Starting with 15kN compaction force and above, friability for type A and type B was less than 1%. It can be determined that the friability of type A is higher than type B. This is expected because hardness levels in type A are greater than type B (Yu, et al., 1988). At all compaction forces (15, 30 and 45kN), the difference between type A and type B were statistically significant ($P<.001$) at 15 and 30kN, and ($P=.002$) at 45kN

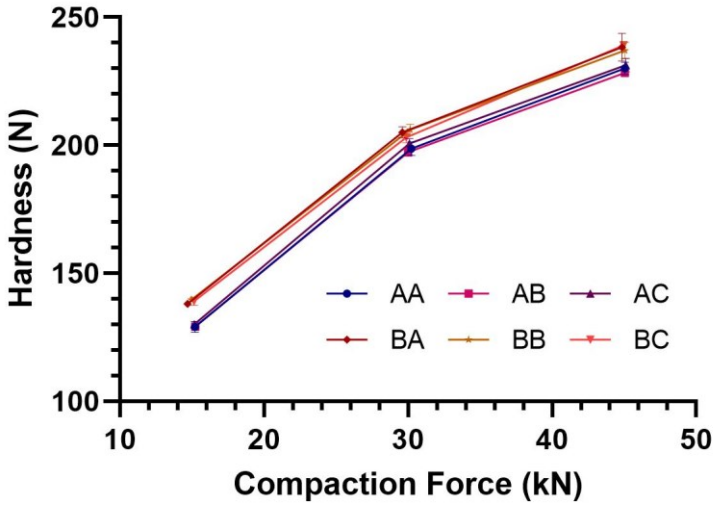
***Tablet Hardness***

It is evident in (Figure 22) that the hardness values of both types are increasing along with the progressive increase of the compaction force. It is shown that type A has lower hardness values than type B. Mesh size 18 has been used for type A resulted in smaller granular size compared to larger granules for type B, where mesh size 12 has been used. In normal conditions, it is known that larger granules will show a decreased hardness because of decreased surface area that leads to weak inter-particulate bonds; thus, lower crushing forces are enough to cause a diametric fracture (Okor, et al., 1998; Adolfsson, et al., 1997). However, in this case, type A, which has smaller granules, had lower hardness values while type B that constitutes larger granules, showed higher hardness values. This is considered a consequence of the formulation composition differences between Type A and type B or due to the different methods of excipient addition used during wet granulation processing (Jubril, et al., 2012). The differences between the averages of batches of both types were statistically significant ($P<0.001$), ($P=.011$) and ( $P=0.001$) at all of the compaction forces applied 15, 30 and 45kn respectively. On the other hand, there was no significant difference between the batches of each type ($P=0.48$) at 15kN, ($P=.62$)

at 30kN, and (*P*=.41) at 45kN for type A batches / *(P*=.54) at 15kN, (*P*=.67) at 30kN, and (*P*=.86) at 45kN for type B batches.

Figure 22

*The Relation between Compaction Force (kN) and Hardness (N) for Type A Batches and Type B Batches (n=3)*

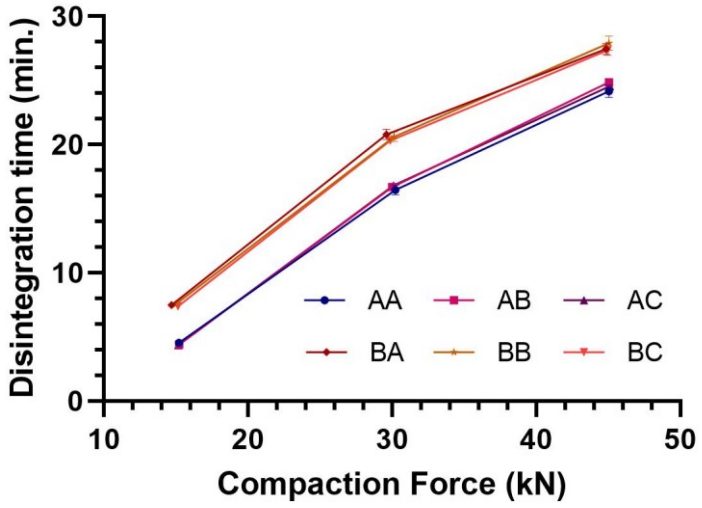



***Tablet Disintegration Time Test***

In (Figure 23) it is shown that type B required more time to be disintegrated than type A at each compaction force that has been applied to the powder. Type B has higher hardness values than type A, leading to disintegration time delay. At all compaction forces (15,30 and 45kN) the difference between type A and type B were statistically significant (*P*<.001 at all compaction forces). On the other hand, there was no significant difference between the batches of each type (*P*=.09) at 15kN, (*P*=.43) at 30kN, and (*P*=.12) at 45kN for type A batches / (*P*=.67) at 15kN, (*P*=.38) at 30kN, and (*P*=.47) at 45kN for type B batches).

Figure 23

*The Relation between Compaction Force (kN) and Disintegration Time (min.) for Type A Batches and Type B Batches (n=3)*




**Evaluation of the Result with MODDE:**

The summary of fit - PLS is given in (Figure 24) Along with (
Table 17) which demonstrates the exact levels of each statistical parameter. Summary of fit provides a review of the basic model statistics where they are presented in four parameters as R2, Q2, Model validity, and reproducibility, where 1 or 100% is perfect. R2 values were 0.961, 0.891, and 0.976 for hardness, friability, and disintegration, respectively.

Q2 for hardness and disintegration was above 0.9, which indicates a very good model. Disintegration had a Q2 of 0.972 as the highest value between the three responses, hardness takes second place with a Q2 of 0.954, and at last friability with a Q2 of 0.871 as the lowest value. Although the friability Q2 value was the lowest, the important thing is having less than 0.3 difference between R2 and Q2 to ensure good model statistics. R2 for friability was 0.891, so the difference is only 0.019.

For hardness, friability, and disintegration, model validity was -0.2 due to almost identical replicates. In this case, the goodness of a model can be ensured by checking the Q2 levels of the responses. If Q2 is nearly or greater than 0.9, the goodness of a model is

guaranteed. The reproducibility of each response was as follows: 0.996, 0.966, and 0.995 for hardness, friability, and disintegration, respectively.

Figure 24

*Summary of Fit - (PLS)*

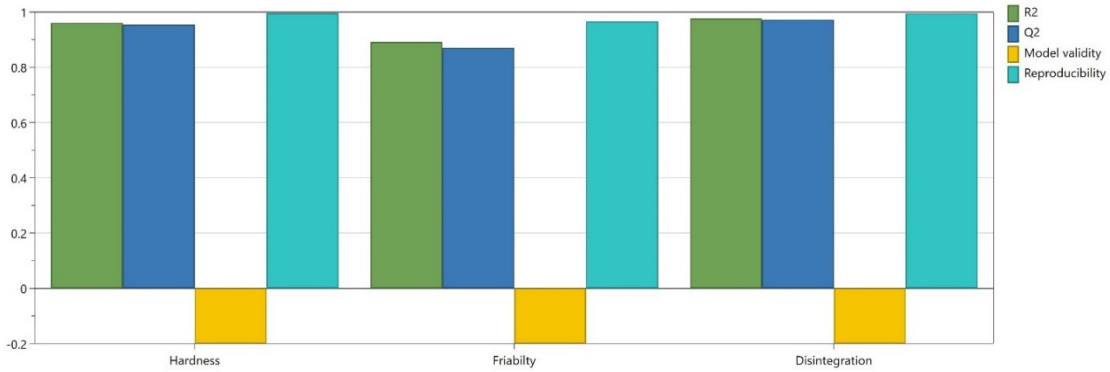



Table 17.

*Summary of Fit - (PLS)*

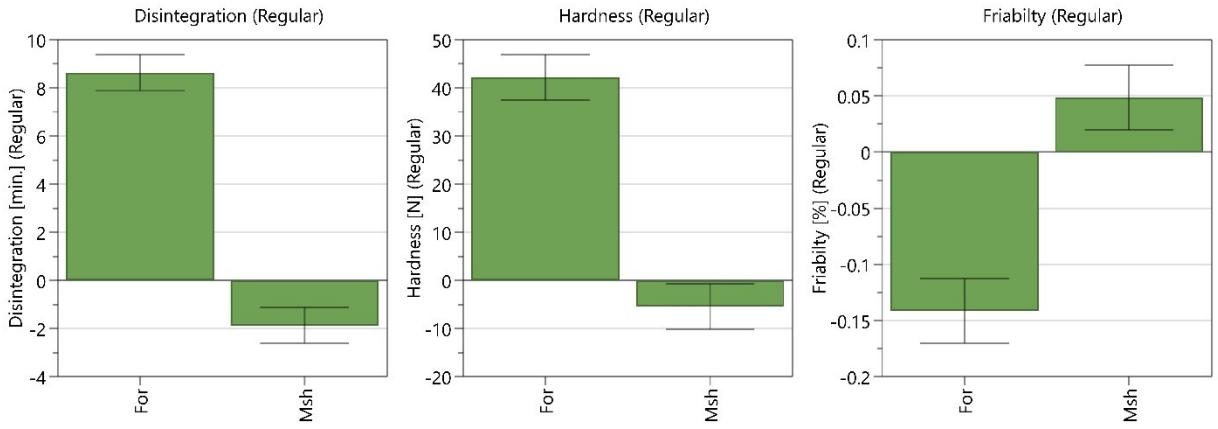
| X Label | Num | R2 | Q2 | Model validity | Reproducibility | |
|---|---|---|---|---|---|---|
| **Hardness** | 1 | 0.961003 | 0.954245 | -0.2 | 0.996394 | |
| **Friability** | 2 | 0.891705 | 0.871041 | -0.2 | 0.966263 | |
| **Disintegration** | 3 | 0.976479 | 0.97295 | -0.2 | 0.995267 | |

***Regression coefficient***

As seen in (Figure 25), the regression coefficients plot indicates both compression pressure and mesh size are significant model terms in all models (Hardness, Friability and Disintegration time). Increasing mesh size has a negative impact on hardness and disintegration. It relatively increases the friability of tablets, unlike the previous scientific literature, which declares that increasing mesh size leads to decreased particles size, which in turn increases the hardness levels and disintegration time (Rajani, et al., 2017; Almaya & Aburub, 2008). And, in accordance to previous scientific knowledge, an increase in compression force which led to increased hardness, causes a reduction in friability and delay the disintegration time (Yu, et al., 1988; Khan & Rhodes, 1976).

Figure 25.

*Overview Plots for Model Evaluation of Disintegration, Hardness and Friability for The Values of the Regression Coefficients of the Model Equation*

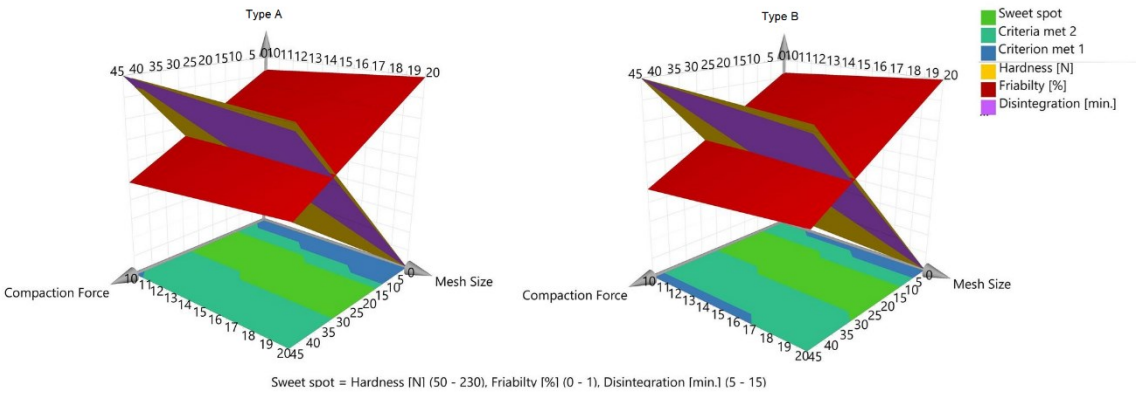



***Sweet spot plot***

As (Figure 26) shows, 3D sweet spot plots for both types were obtained. The mesh size range was set as (10 – 20), the compaction force range started from 0 to 45kN. The increase of compaction force leads to an increase in the hardness and disintegration and a decrease in friability for both types. The change in all of the three responses due to compaction force increase shows a high degree slope. Also, the increase of mesh size leads to an increase in friability and a decrease in hardness and disintegration. The change of the three responses due to mesh size increase shows a low degree slope. It is noticeable that the sweet spot (green area) range for type A have higher compaction force demand than it is in type B.

Figure 26

*3D Sweet Spot Plots for Type A and Type B*

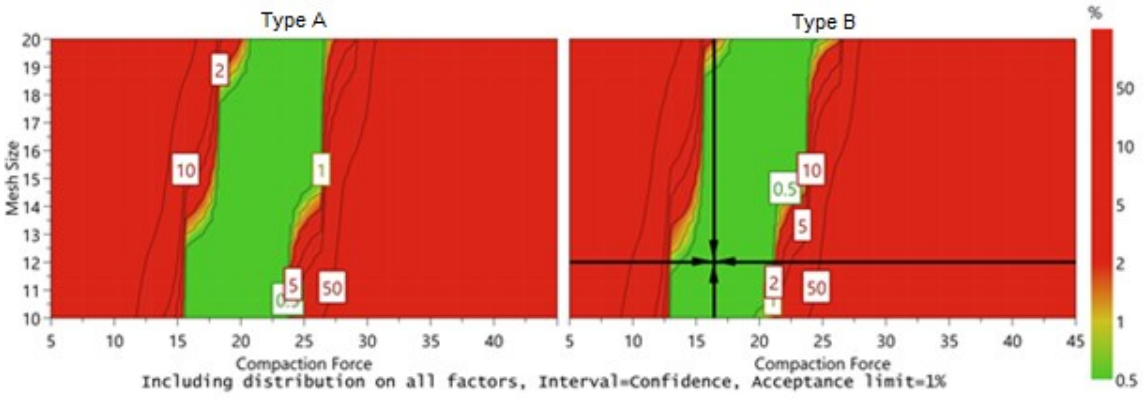



***Design space***

Design space was obtained after applying all the factors according to their specific ranges based on QTPP requirements of the Paracetamol tablet. Both Types were applied to the MODDE program, and the design space study is shown in (Figure 27). It is noticed that mesh size is directly proportional to compaction force in both Types to achieve critical quality attribute requirements. Obviously, Type A demands higher compaction force levels than Type B to meet the Paracetamol tablet's critical quality attributes when using the same mesh size.

Figure 27

*Design Space - (PLS) Probability of failure (%) for Friability and Disintegration - Optimizer Set-point (R)*



A variety of variability sources are considered in the estimation process that can affect the size of the design space. The acceptance limit is set at 1%, and the colours illustrated in the (Figure 27) resembles the percentage of failure in that particular area.

The green zone (known as the operating range) have high confidence intervals because it has less than 0.5% failure percentage, which means that a formulation from the green zone could guarantee the quality of the final product.

The yellow zone (known as the acceptable range) resembles the zone of low confidence intervals due to its failure percentage being 0.5% to 1%. An acceptance for a formulation from this zone could be claimed, but it will not fulfil the desired specifications.

The red zone stands for the area where the failure percentage is above 1%, which leads to an unacceptable formulation that does not reach the desired specifications. Design space illustrates that when raising the mesh size, compaction force should be increased in order to obtain the best results.

The robust set-point shows the optimal conditions or the best compromise as set-point. It is available if the prediction of all responses within their limits is achievable based on Monte Carlo simulations. The robust set-point is demonstrated in the design space plot by crossed arrows. It is worth mentioning that the robust point should contain the lowest log (D), where D is the overall distance to the target. (Table 18,

Table 19) below are showing the exact values of the CPPs and the CQAs where the robust point is predicted.

Table 18.

*Process Parameters for Robust Set-Point*

| Factor | Role | Value | Graph | Factor contribution |
|---|---|---|---|---|
| **Compaction Force** | Free | 16.4286 | | 87.7296 |
| **Mesh Size** | Free | 12 | | 12.2704 |
| **Method of Excipient Addition** | Free | Type B | | |

Table 19.

*Quality Attributes for the Robust Set-Point*

| Response | Criterion | Value | Graph | log(D) | Prob. of failure | Cpk |
|---|---|---|---|---|---|---|
| **Hardness** | Predicted | 147.516 |  | | | |
| **Friability** | Target | 0.846941 |  | -0.619957 | 0% | 1.96588 |
| **Disintegration** | Target | 9.37339 |  | -1.80394 | 0% | 1.8433 |

# CHAPTER V

## Conclusion and Recommendations

We conclude from our results that type B (12 mesh) of DC grade Paracetamol powder had better compressibility (Carr's index) and flowability (Hausner's ratio), less plastic and elastic energy, less ejection force requirement and more densified tablets (Heckel plot) than type A. On the other hand, type A required less rearrangement energy than type B.

In type A, batch to batch variation was observed in rearrangement and elastic energies during compression cycle.

When QbD approach and DoE programs were employed, it was found that type B required less compaction force to comply with the intended specifications according to QTPP principles of Paracetamol tablet, and to reach the maximum quality level of the final product.

The results in the program showed that if we compress Type B DC Paracetamol powder at 16.4kN compaction force, that will result in tablets that reach the desired characteristics based on QTPP standards for Paracetamol tablet without adding any excipient.

It was concluded that type B DC grade paracetamol with own formulation in comparison to type A, will result in the best quality assured tablet without addition of external excipients for tableting when viewed from a formulator standpoint.

**Recommendations for further research:**

Paracetamol Tablet pharmaceutical formulation studies can be designed and evaluated with direct compression method. Study design could be filler type and amount to have more understanding of type A compressibility.

It could be possible to add lubricants to decrease the inter-particulate friction or the friction between the particles and the die wall.

Other studies could investigate the effects of the compaction speed on the compaction behaviour of the Paracetamol powder.

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# APPENDICES

## Appendix A.

## Comparison of the Tableting Properties of Pre-Processed Paracetamol Powders by Using QbD Approach by Compaction Simulator

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**Comparison of the Tableting Properties of Pre-Processed Paracetamol Powders by Using QbD Approach by Compaction Simulator**

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# Comparison of the Tableting Properties of Pre-Processed Paracetamol Powders by Using QbD Approach by Compaction Simulator


## Abstract

Pre-processed active pharmaceutical and excipient usage have been widely spreading in recent years. Active Pharmaceutical Ingredient producers are inclined to producing a pre-processed form of powders that are poorly compressible to improve their chemical and physical characteristics. With the application of the Quality by Design approach during the development of active ingredients in the pharmaceutical industry, these companies could assure the quality of the end product without spending more time for reproducing the pre-processed from the beginning. This study aims to employ the Quality by Design approach to develop and improve the quality of paracetamol contains tablets with the optimal Critical Process Parameters by using two different types of paracetamol. Critical Quality Attributes and Critical Process Parameters were identified according to risk assessment results. The chosen Critical Quality Attributes and Critical Process Parameters were included in the creation of a design space. Minitab 18 and Modde programs were used to identify the Critical Process Parameters effect on Critical Quality Attributes and the degree of their effects using factor effect plots, contour plots, and sweet spot plots were done based on these artificial intelligence programs. For the best product outcome, the study showed that using a smaller mesh size with intra-granular pre-gelled starch inclusion in a specific range of compaction force will generate a higher quality product with the best powder flow characteristic and the best tableting properties.


**Keywords:** Paracetamol; Pre-processed; Quality by Design; Design of Experiment; Critical Quality Attributes; Critical Process Parameters; Risk Assessment; Compaction simulator.

## INTRODUCTION

Paracetamol (APAP) is a long-invented, antipyretic analgesic, which is a broadly prescribed and used drug worldwide. It is an analgesic that is used to ease the pain and fever in both adults and children [1]. Although the production of high-quality APAP tablets gained tremendous significance because of their extensive usage, APAP powders have the characteristic of a poorly compressible material which is the reason for adding the excipients that improve the compressibility of the powder [2]. This is one of the reasons why many powder manufacturers are competing to produce the best pre-processed APAP powder and finding the best way to process its formulation to yield high-quality paracetamol tablets. One of the tablet manufacturing technics of the tablets which contain APAP powder is wet granulation processing. Wet granulation is a technique where particle size enlargement occurs by agglomeration of powders [3]. There are a variety of advantages that come along with wet granulation processing such as increase the compressibility of the powder, improvement of the flow-ability, and lower the amount of dust during manufacturing, transferring, and storage processes [4, 5]. Several tests should be applied for the quality assurance of the product. In the pharmaceutical industry in the past decades, it was known to assess the quality after the final product was produced which was a time-consuming method. Furthermore, in case of failure of the test the whole batch was disposed of and the manufacturing of a new product was started from the beginning [6]. On the way of pharmaceutical industry development, other sciences such as mathematical sciences, electronic and technical technology along with pharmaceutical technology crossed over and gathered to provide less time consuming, cost-saving, and higher quality assurance methods of producing a certain drug product.

The method produced by the combination of these sciences is Quality by Design (QbD) which allows assuring the quality of a product before the actual production by using technological instruments to apply the factors that affect the quality and statistics to increase the reliability of the results [7,8]. QbD is defined as a systematic, risk-based,

and scientific approach that begins with predetermined goals and gives prominence to the product, process understanding, and process control based on risk assessment techniques [9]. It also involves an advanced scientific comprehension of critical process and final product characteristics by designing controls and tests depending on scientific boundaries of understanding defined during the development phase and using the previous knowledge gained by the previous productions to enhance its quality [10]. The implementation of QbD in the pharmaceutical area has been described and illustrated in the ICH guidelines (International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use) ICH Q8 (pharmaceutical development), ICH Q9 (quality risk management), ICH Q10 (Pharmaceutical quality system), and ICH Q11 (development and manufacture of drug substances). These provide remarkable guidelines regarding the scope and definition of QbD and the requirements of its usage in the pharmaceutical industry [11]. The concept of QbD consists of several steps that should be fulfilled and appropriately completed. The first step is to define a quality target product profile (QTPP) according to a prior scientific knowledge. The second step is the identification of critical quality attributes (CQAs) and critical process parameters (CPPs). Thirdly, studying risks on the product's quality. Fourthly, the establishment of multivariate experiments by using Design of Experiments (DoE) to identify the relationships between CQAs and CPPs and to develop a design space. Finally, controlling the manufacturing process and operating within the yielded design space for the product quality assurance [12].

In our study 2 types of pre-processed paracetamol powder with the same formulation but different wet granulation preparation processes, have been used to study the differences between the two different powder preparation processes and to find the optimal CPPs to generate the best and quality assured drug product. 3 batches from each type were included in the study to compare the difference between batches results from the same type and to compare the two types with the most accurate results possible. A compaction simulator was used in the compression of the pre-processed paracetamol powder to prepare the tablets. A compaction simulator is a machine that

was designed specifically for simulating and mimicking the precise tableting cycle process and is capable of recording all the significant parameters during the compaction process [13, 14]. CQAs were identified according to the published articles [15, 16] and USP 32 [17]. CPPs were chosen as the most important parameters that significantly affect the CQAs. Modde Pro 12.1 (Sartorius, Sweden) and Minitab 18 statistical software (Minitab Ltd, UK) programs were used to determine the CQAs and CPPs to establish a controlled design space and to found the optimized formulation of APAP.

## MATERIALS AND METHODS

### Materials

In this study, two types of pre-processed paracetamol powders were used and these powders were gifted from (Atabay Fine Chemicals, Turkey). Pre-processed APAP contains 90% of paracetamol and 10% excipients like binder, disintegrant and lubricant. All excipients are pharmaceutical grade.

### Methods

#### Preparation of Pre-Processes APAP Granules

APAP powders were prepared by using wet granulation technic. There are two types of granules and they have essential differences in the processing between type 1 and type 2. The first one is type 1, the whole amount of diluent excipient was added during powder mixture, before wetting the granules (intra-granular), while in type 2 diluent excipient was divided into two parts and added in two different steps, the first part was added before wetting the granules (intra-granular) and the second part was added in the final mixing phase after sieving the dried powder (extra-granular).

The second difference between two type of APAP powder was the mesh size used in the final sieving of dry powder for the sake of specifying a particular granular size, a mesh size of 18 has been used in Type 1 and 12 Mesh size was used regarding Type 2 sieving.

**Elements of QbD**

**Determination of Critical Quality Attributes (CQAs)**

CQAs are one of the QbD elements that help in ensuring the best outcome of a product when they are met. They are the physical, chemical, biological, or microbiological aspects or features that are confined to a certain range which should be studied and controlled in order to achieve the desired product quality [18]. For a solid dosage forms, the purity, dose strength, drug release, and stability are affected by CQAs. Hardness and disintegration were identified based on the initial screening studies on the market product quality parameters while friability was based on USP standards for oral tablet dosage forms. CQAs chosen for this study were hardness, friability, and disintegration as they are the most effective attributes to solid dosage forms.

**Risk Assessment**

Risk assessment is another element of the QbD that is concerned in identifying the process parameters and analyzing their effects on CQAs of the final product to conclude which of them are critical process parameters that should be included in the DoE study and which of them are non-critical and will be avoided [19]. Our current knowledge along with literature and ICH Q9 risk management guidelines were the main bases in which risk ranking determination was based on. The impaction on the final drug product quality of each critical process parameter that has been chosen to be included in this study was the cornerstone for estimating the risk ranking of each CPP. The risk ranking of the CPPs are categorized as low, medium, and high. Normally, those with low risk were excluded from the DoE study while medium and high-risk CPPs were included in the study as independent factors [19, 20]. Critical quality attributes (CQAs) have been identified based on the risk assessment prediction of final product failure if matching the CQAs was not achieved. Risk assessment clears the effects of each CPP on each CQA individually which made it possible to determine the independent factors that are included in the DoE experimental study [21], and the same approach was applied in our study during the decision of critical parameters. CPPs that have been chosen in

this study are compaction force, mesh size, and pre-gelled starch addition method are shown in the Table 1 with their risk rankings.

**Table 1: Risk assessment of the input and process parameters against the CQAs**

| Process Variables | CQAs | | |
|---|---|---|---|
| | **Hardness** | **Friability** | **Disintegration** |
| **Compaction Force** | High | High | High |
| **Addition of Pre-gelled starch** | High | Medium | High |
| **Mesh Size** | High | Medium | High |

**Design of Experiment**

DoE is the highly systematic branch of the QbD that illustrates the relationship between the independent variables CPPs and the dependent variables CQAs to reach the optimal process characteristics and drug product quality [8, 22]. Systematic variations of the CPPs and their simultaneous effects on the CQAs allows DoE to provide the maximum possible amount of information with the minimum amount of experiments [23]. Design space is defined according to ICH Q8 as an established multi-dimensional area of input variables and CPPs demonstrated to provide assurance of quality [18]. Multi-level factorial design methodology was implemented to evaluate tablet properties. 3 batches from each type were compressed at three different forces 15 (-1), 30 (0), and 45 (+1) kN as an approximated values and the mean values were used as input data's. Briefly, In the study, 3 different compression forces of APAP granules having 2 different mesh sizes were prepared to be a total of 18 pieces, from 3 series of each one. To be assured about the final product quality the results of these applications were used to form a controlled and well-defined design space. The details of the study is given in Table 2.

**Table 2: Multi-level Factorial Design Details**

| Multi-level Factorial Design | | | |
|---|---|---|---|
| **Design Summary** | | | |
| **Factors:** | 2 | **Replicates:** | 1 |
| **Base runs:** | 6 | **Total runs:** | 6 |
| **Base blocks:** | 1 | **Total blocks:** | 1 |
| **Number of levels: 3; 2** | | | |
| **Factors** | | | |
| **Compression force (kN)** | **US Mesh size** | **Addition of pre-gellatinized starch** | |
| 15 (-1) | 12 (-1) | Two step add. | |
| 15 (-1) | 18 (+1) | One step add. | |
| 30 (0) | 12 (-1) | Two step add. | |
| 30 (0) | 18 (+1) | One step add. | |
| 45 (+1) | 12 (-1) | Two step add. | |
| 45 (+1) | 18 (+1) | One step add. | |

Minitab 18 statistical software (Minitab Ltd, UK) and Modde (Umetrics, Sweden) programs were used to evaluate data and to decide optimized formulation.

**Tableting Process**

A compaction simulator (Stylcam R200, Medelpharm, France) was used to press tablets, this equipment gives the most effective results to evaluate compressibility with the small amount of powder [13, 24]. Machine Speed was 10 rpm and simulated machine was Fette 102i (Euro B - 28800 Tab/Hour) with an 11.28 mm round and flat-faced Euro B punch was used for compacting the powder to form the tablets. 100 g from each powder sizes were taken by using (Mettler Toledo AB 104-S/PH analytic balance) and 20% of extra powder was added to account for the lost powder during the compaction

procedure. 20 tablets from each batch of the 6 batches were pressed for each compaction force (15, 30, and 45 kN). Die filling was done with automated filling. Subsequently, physicochemical tests were performed on the pressed tablets.

**Analysing of the Powder Characteristics and Tablet Physicochemical Properties**

In the study, although the aim was to evaluate tableting properties with the compaction simulator, the flow properties of prepared powders were also tested to have an idea about the powder properties. The prepared powders were investigated; their true density, bulk density, tapped density, Hausner ratio and Carr index (%) values were analysed, respectively. The flow properties were evaluated according to USP 39 [25].

For all formulations, tablets were weighed by using analytical precision balance (Mettler Toledo AB 104-S/PH, Switzerland), and mean weight and standard deviation values were calculated for each formulation [26].

The thickness and diameter values of tablets were measured by an automatic caliper (0-150 mm TCM, Tchibo, Germany) and the results were recorded.

The hardness test of the pressed tablets were measured by using TBH 225 device (Erweka, Germany). The tablets mean hardness (N) and SD (±) values were calculated [27].

The Friability test was performed for each test group. The tablets were weighed and placed into the friability tester (TAR 220, Erweka, Germany) for 4 min at 25 rpm and at the end of the test tablets were reweighed and weight losses were recorded [28].

To measure the disintegration time of tablets 1000 mL purified water was filled in the beaker of disintegration test device (240 ZT 322, Erweka, Germany) and the equipment temperature was set to 37.00 ± 0.5 °C. The disintegration time of tablets were observed

visually, the time when all the tablets were dispersed was considered as the disintegration time [29].

## RESULTS

### Powder Characterization Test Results

A characterization studies of the APAP powder mixtures were performed. The test results are shown in the Table 3.

**Table 3: APAP powder properties**

| US Mesh Size | Bulk density (g/ml) | Tapped Density (g/ml) | Hausner Ratio | Carr Index % |
|---|---|---|---|---|
| **Type 1- 18 mesh** | 0,607± 0,006 | 0,700± 0,005 | 1,159± 0,021 | 13,74± 1,52 |
| **Type 2- 12 mesh** | 0,627± 0,006 | 0,680± 0,000 | 1,085± 0,010 | 7,85± 0,85 |

The obtained Carr index (%) values and Hausner ratio values of this two type powders are significantly different. According to the US Pharmacopeia, smaller Carr Index (%) and Hausner Ratio values indicate better flow [30].

### Tablet Physicochemical Test Results

The physicochemical test results of the 6 formulations are given in the Table 4. Standard deviation values of 3 series prepared in each formulation group are also given in Table.

**Table 4: The physicochemical properties of the formulations.**

| Factors | | | Responses | | |
|---|---|---|---|---|---|
| **Compression force (kN)** | **US Mesh size** | **Addition of pre-gellatinized starch** | **Hardness mean (N) ± SD** | **Disintegration time (min.) mean ± SD** | **Friability (%) mean ± SD** |
| 15 (-1) | 12 (-1) | Two step | 137 ± 2,1 | 7,7 ± 0,4 | 0,87 ± 0,02 |
| 15 (-1) | 18 (+1) | One step | 126 ± 3,0 | 3,8 ± 0,4 | 1,01 ± 0,04 |
| 30 (0) | 12 (-1) | Two step | 205 ± 2,5 | 20,4 ± 0,6 | 0,64 ± 0,03 |
| 30 (0) | 18 (+1) | One step | 193 ± 4,7 | 16,8 ± 0,5 | 0,72 ± 0,00 |
| 45 (+1) | 12 (-1) | Two step | 236 ± 2,2 | 27,9 ± 1,0 | 0,57 ± 0,02 |
| 45 (+1) | 18 (+1) | One step | 228 ± 1,7 | 24,7 ± 0,7 | 0,63 ± 0,04 |

The hardness and the disintegration time values of the formulations which were prepared with 12 US Mesh Size are higher than the formulations prepared with 18 US Mesh Size, however, the friability value of these formulations are lower.

**Evaluation of the Data with Artificial Intelligence Programs**

All data were evaluated with Minitab 18 and Modde Pro 12.1 programs, respectively.

**Evaluation of The Result with Minitab**

In the study, the effects of the independent variables mesh size and compaction force on the hardness value, disintegration time and friability (%) values, which are the

dependent variables, were evaluated. Pareto charts were prepared and the effects of independent variables on dependent variables were examined. Values with a P value below 0.05 were considered as statistically significant. Pareto graphics of the variables are given in Figure 1.

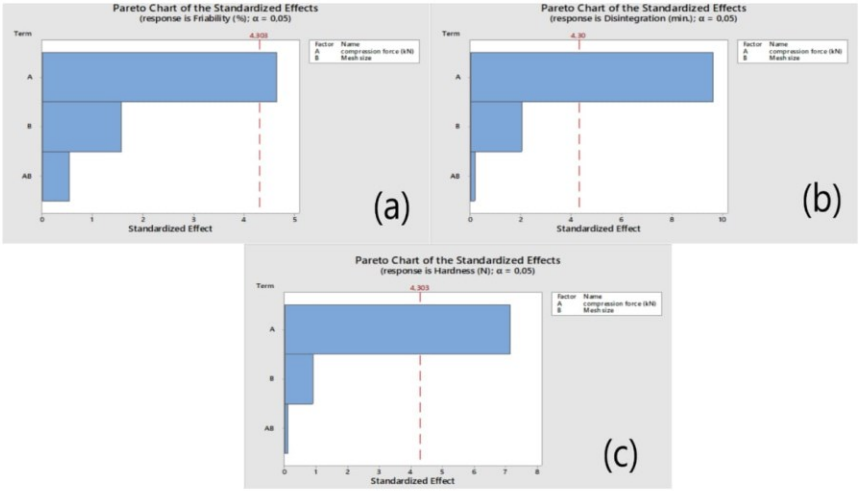


**Figure 1: The Pareto Charts of variables (a): The effect of independent variables on friability; (b): The effect of independent variables on disintegration time; (c): The effect of independent variables on hardness**.

**Table 5: Real and Adjusted $R^2$ values of the mathematical models**

| Dependent Variables | Real $R^2$ (%) | Adjusted $R^2$ (%) |
|---|---|---|
| Hardness | 96,29 | 90,72 |
| Friability | 92,41 | 81,02 |
| Disintegration time | 97,98 | 94,94 |

Contour plot graphics showing the relationship of compression force and mesh size on hardness, friability and disintegration time are given in Figure 2.

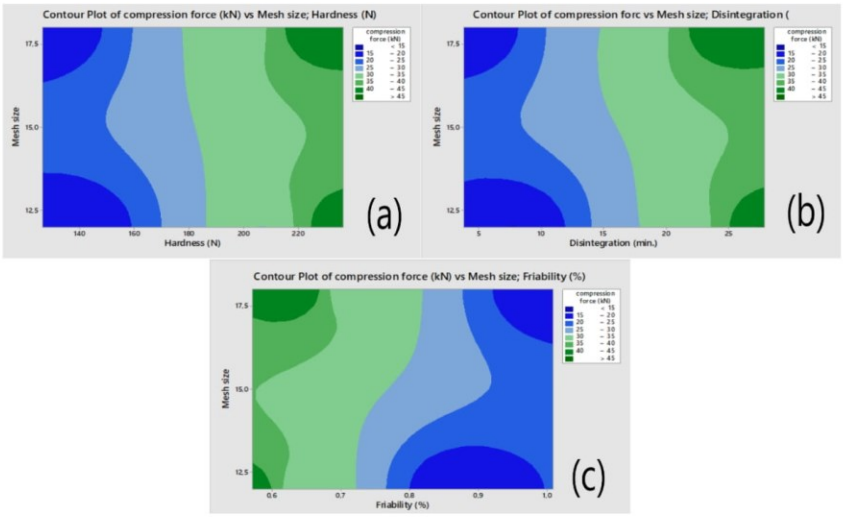


**Figure 2: Contour Plot graphics on dependent variables versus independent variables (a): Mesh size and compression force effect on Hardness; (b): Mesh size and compression force effect on Disintegration time; (c): Mesh size and compression force effect on Friability.**

The optimization study was done on Minitab with the obtained data and the program suggested the parameters given in Table 6.

**Table 6: Optimization study results**

| Compression Force (kN) | Mesh Size | Friability (%) | Disintegration time (min.) | Hardness (N) |
|---|---|---|---|---|
| 28,33 | 12 | 0,7111 | 17,5469 | 187,529 |

According to these findings, the granule should be sieved through 12 mesh size and the compression force should be 28.33 kN to achieve the desired formulation.

**Evaluation of The Result with Modde**

An experimental design study was conducted to observe the effect of variable changes on the critical outputs and experimental data evaluated using Modde Pro 12.1 statistical modelling program that allows optimization. The experimental data obtained from direct compression method were uploaded to Modde, then an optimum formulation was suggested by the program. Using the Partial least squares regression (PLS) experimental data were fitted in statistical module of Modde 12.1 Pro. Also, the validity of the experimental design was checked by the analysis of variance (ANOVA) test [31]. The statistical parameters determined were R2, representing the variation explained by the model, and Q2, the fraction of the variation of the response that can be predicted by the model. Moreover, the validity of the model and experimental design was checked by ANOVA test. A model with R2 lower than 0.5 is a model with rather low significance. Q2 should be greater than 0.1 for a significant model,for a good model it must be greater than 0.5 and the difference between R2 and Q2 should also be smaller than 0.3 . The summary of PLS is given in Figure 3.

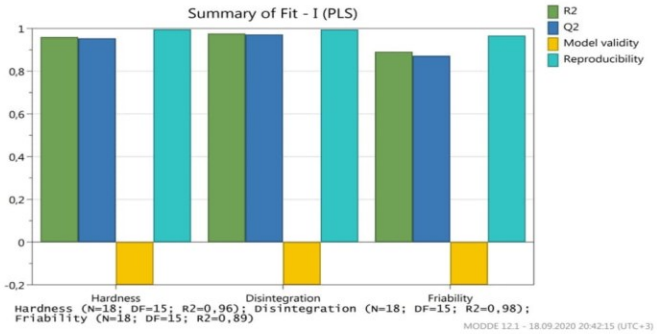


**Figure 3: Summary of fit PLS Model**

The coefficient plot presents a graphical representation of the model terms in order to determine their significance and indicate the magnitude of the effects of process variables on the responses, while their sign indicates a positive or a negative influence on the response. A significant term is one with a large distance from y=0 as well as having an uncertainty level that does not extend across y=0. The list of PLS model is given in Table 7.

**Table 7: List of PLS Model fit**

| | $R^2$ | $R^2$ Adj. | $Q^2$ | SDY | RSD | Model Validity | Reproducibility |
|---|---|---|---|---|---|---|---|
| **Hardness** | 0,96 | 0,95 | 0,95 | 43,41 | 9,22 | -0,2 | 0,995 |
| **Disintegration** | 0,97 | 0,97 | 0,97 | 8,92 | 1,47 | -0,2 | 0,995 |
| **Friability** | 0,89 | 0,88 | 0,87 | 0,16 | 0,06 | -0,2 | 0,966 |

Figure 4 illustrates the regression coefficients of the model equations which help in determining the significance of compression pressure and mesh size in the models included in the study.

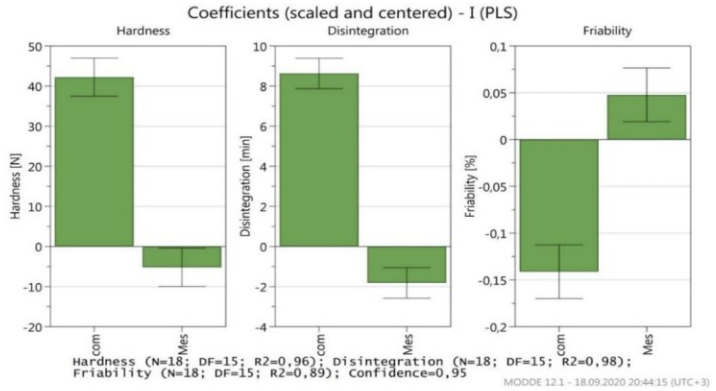


**Figure 4: The values of the regression coefficients of the model equations (Com: Compression pressure; Mes: Mesh size).**

The Modde program was trained to find optimum formulation and optimized process parameters suggested by Modde Pro 12.1 is given in Figure 5.

| Response | Criterion | Value | Graph | log(D) | Prob. of failure | Cpk |
|---|---|---|---|---|---|---|
| **Hardness** | Predicted | 179,121 | | | | |
| **Disintegration** | Minimize | 15,8301 | | 1,40771 | | |
| **Friability** | Minimize | 0,74114 | | 1,48083 | | |

| Factor | Role | Value | Graph | Factor contribution |
|---|---|---|---|---|
| **compression force** | Free | 25,8574 | | 82,0072 |
| **Mesh size** | Free | 12,0005 | | 17,9928 |

**Figure 5: Optimized process details of Modde**

The modde program recommends 12 as the mesh size and 25.8574 as the pressure force.

## DISCUSSION

According to APAP powder properties results the type 2 formulation shows better flow properties than type 1. The Bulk density of the powders depend on the particle size and

shape of the powders, therefore the bulk density value of the Type 1 APAP formulation was found lower than the Type 2 [32]. Also, the physicochemical properties of the formulations illustrate that the results are compatible with the general information that the particle size increases, the hardness value decreases, and the friability increases [33]. Moreover, the standard deviation values are low, and the series are also compatible with each other.

Evaluation of the results with Minitab showed that pressure force has a significant effect on all dependent variables. Although the degree of significance is not high, it is possible to say that the mesh size has a greater effect on the friability % than other dependent variables and the closeness of the real R2 value found to the adjusted R2 value indicates that the model is fit [34]. While when evaluating the results with MODDE, it was found that R2 and Q2 values for each output are higher than 0.5 and the differences between the two values are smaller than 0.3. Although, the model validity is less than 0.25 poor reproducibility values are in acceptable range since there are some statistically insignificant (RSD %) differences between compression forces applied on the batch. It was noticed that hardness and disintegration are negatively affected by Increasing mesh size; and the friability of tablets is relatively increased. And, in accordance with previous scientific knowledge increase in compression force which led to increased hardness causes a reduction in friability which delays the disintegration time [33].

Both programs gave the data that a value of 12 mesh size and pressure force between 25-30 kN is more appropriate.

As seen in the study, the effects of powder particle size on tableting are quite high. According to the findings obtained with both programs, 12 and 18 mesh sizes show different tableting and powder properties. The programs show us that the 12 mesh size inherently provides better powder properties. It is possible to obtain tablets with desired physicochemical properties even at lower compression forces. However, by making improvements in 18 mesh, such as addition of appropriate excipients, it will become a more suitable candidate.

It has been seen that it is possible to examine powder and tablet properties much more effectively with such as statistical programs. Such programs used in the pharmaceutical industry make a great contribution to the applications during the QbD approach and provide the desired quality for both active substance and drug manufacturers in a short time [35].

## CONCLUSION

It is extremely important to work on formulation properties by using such statistical programs in factories that produce pharmaceuticals, especially in R&D departments. The automotive industry and the aircraft industry have been using these applications for a long time, and since the pharmaceutical industry does not want to change their routine application, implementation is delayed.

However, as can be seen in this study, it will be much more effective to use this type of statistical software that can be used in faster manner instead of conventional measurements or approaches.

In our study, by using statistical software's, it was possible to evaluate the powder properties and tablet properties of APAP in 2 different mesh sizes, 12 and 18, in a very short time, and it was determined that the 12 mesh size provided the desired tablet properties without any need of excipients in the range of 25-30 kN pressure force.

## ACKNOWLEDGMENTS

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## CONFLICT OF INTEREST

No conflict of interest associated with this work

## CONTRIBUTION OF AUTHORS

We declare that this work was done by the authors named in this article and all liabilities pertaining to claims relating to the content of this article will be borne by the authors

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## Appendix B.

## Curriculum Vitae

# MUSAAB MAHMOUD SAADA

## Personal Information

**Date of Birth:** Sep. 27th 1989
**Nationality:** Syrian
**Status:** Single
**Address:** Gümüşhane - Turkey
**Mobile Phone:** (0090) – 551 - 0363397
**Email**: musaabmds@yahoo.com

## Education

- **2017- 2021** Near East University
  Ph.D Pharmaceutical technology
  **Thesis:** Using Compaction Simulator and Design Of Experiment (Doe) Approach; Characterization And Evaluation Of Direct Compressed Paracetamol Powder.

- **2013 – 2015** Al Zaytoonah Private University of Jordan
  MSc Pharmaceutical Science
  **Thesis:** Pharmacophore-Based Screening and Identification of Novel Phosphoinositide 3-kinase (PI3Kα) Inhibitors

- **2007 – 2013** Jordan University of science and technology (JUST).
  BSc Pharmacy

## Experiences

- **2019-2020:** Had a Part-Time job as a Lab assistant in Near East University – Pharmaceutical Technology Department.
- **2015-2017:** Had a Full-Time job in Al-Wesam pharmacy.
- **7/5/2011:** Participation in the first conference for students of pharmacy faculties in Jordanian universities that held at University of Jordan
- **21/11/2010:** Participation in the first conference for students of pharmacy faculties in Jordan University of science and technology.

## Skills

- Languages

  Arabic: Fluent. English: Fluent Turkish: Beginner

- Computational

  - Microsoft office and internet
  - Linux and windows operating systems
  - MODDE® - Design of Experiments Software
  - JMP Software from SAS
  - Minitab: Data Analysis

- Prism - GraphPad
- Molecular operating environment program (MOE)
- Pymol
- Ksnapshot and GIMP

- Personal
  Communication skills, team work personality with good management and planning abilities, Active, Hard-worker, disciplined, punctual, ready to improve, Ability to work in high stress environments, and Ready for hard and long-time working.

## Published articles

- Dima A. Sabbah; ***Musaab Saada***; Reema Abu Khalaf; Sanaa Bardaweel; Kamal Sweidan ;Tariq Al-Qirim; Amani Al-Zughier; Heba Abdel Halim; Ghassan Abu Sheikha (2015). Molecular modeling based approach, synthesis, and cytotoxic activityof novel benzoin derivatives targeting phosphoinostide 3-kinase (PI3Ka), **Bioorganic & Medicinal Chemistry Letters**. 25,16, 3120–3124

- ***Musaab Saada***; Yıldız Özalp; Burcu Mesut; Buket Aksu (2021). Comparison of the Tableting Properties of Pre-Processed Paracetamol Powders by Using QbD Approach by Compaction Simulator, **FOURRAGES Journal.** 245(2)

## Laboratory work

- Chromatography (Colum, TLC, HPLC…).
- FT-IR
- Rheometer and Viscometer
- Hardness apparatuses
- Friability apparatuses
- Disintegration apparatuses
- Dissolution apparatuses
- Compaction Simulator

## Scientific Background

- Attend First aid course at the JPA - **10/2013**
- Attend Injection Course at the JPA **- 10/2013**
- Attend Advanced Pharmaceutical Biotechnology at the JUST, **2011**
- Attend Advanced Industrial Pharmacy at the JUST, **2012**
- Attend Communication Skills in Pharmacy at the JUST, **2013**
- Attend Pharmacoeconomic at the JUST, **2013**

## References

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**Appendix C.**

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