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USE OF COMPACTION SIMULATOR TO OBSERVE THE EFFECT OF CO-PROCESSED LACTOSE BASED FILLERS AND LUBRICANTS ON DIRECTLY COMPRESSIBLE IBUPRUFEN BY QUALITY BY DESIGN (QBD) APPROACH

POSTGRADUATE THESIS

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Ph.D Thesis

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Hereby I declare that this thesis study is my own study, I had no unethical behavior in all stages from 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 behavior of breeching patent rights and copyright infringement during the study and writing of this thesis.

NAILLA JIWA

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3. MATERIALS AND METHODS

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LIST OF ABBREVIATIONS

API	Active Pharmaceutical Ingredient
AS	Active Substance
BCS	Biopharmaceutical Classification System
CMA	Critical Material Attribute
CPP	Critical Process Parameter
CQA	Critical Quality Attribute
DOE	Design of Experiments
DS	Design space
DC	Direct compression
WG	Wet granulation
DG	Dry granulation
SP	Spheronization
DPMO	Defects per million opportunities
EP,	European Pharmacopoeia
FMECA	Failure mode, effects and criticality analysis
FMEA	Failure modes and effects analysis
FTA	Fault tracking approximator
FDA	Food and Drug Administration
GMP	Good Manufacturing Practice
HACP	Hazard analysis and critical control points
HCl	Hydrochloric Acid
IR	Immediate Release
ICH	International Conference on Harmonization
ISO	International Standards Organisation
kN	Kilonewton
MgSt	Magnesium Stearate
MCC	Microcrystalline cellulose
MPa	Megapascal
NF	National Formulary
PLS	Partial least squares regression
PSD	Particle size distribution

PIL	Patient Information Leaflet
PHA	Preliminary hazard analysis
PAT	Process Analytical Technology
QbD	Quality by design
QTPP	Quality Target Product Profile
RSM	Response surface methodology
RA	Risk Assessment
RPN	Risk priority number
SEM	Scanning electron microscope
SGF	Simulated gastric fluid
SPC	Summary of Product Characteristics
TS	Tensile strength
USP	United States Pharmacopeia
Py	Yield pressure

OZET

Amaç: Bu calışmanın amacı, "quality by design" kullanılarak formulasyon geliştirmek, istenen ürünün kalite profilini ve kritik ürün özelliklerını tanımlamaktır. "Compaction Simulator" kullanılarak önceden işlemden geçen iki tip laktoz bazlı dolgu maddesinin deformasyon davranışını ve sıkıştırma özelliklerini karakterize edildi. Ayrıca formülasyonlarda lubrikant türü ve konsantrasyonunun verimliliği de belirlendi.

Gereç ve yöntem: Bu çalışma için %85 İbuprofen ve %15 eksipiyan içeren önceden granüle edilmiş bir doğrudan sıkıştırma ürünü olan Ibuprofen DC 85W seçilmiştir. Dolgu maddesi olarak Cellactose®80 ve MicroceLac®100 kullanıldı ve lubrikant olarak Magnezyum Stearat, Stearik Asit ve Sodyum Stearil Fumurat kullanıldı.

Formülasyona çeşitli dolgu maddeleri ve lubrikantlar eklenerek ilacın genel kalitesinin kritik kalite özelliklerini nasıl etkilediğinin daha iyi anlaşılabilmesi için QbD kullanıldı.

Bilindiği gibi ürün geliştirme oldukça karmaşık, bilgi gerektiren ve zaman alan bir prosestir. İlaç ürününün formülasyonunda doğru işlevselliğe ve karşılık gelen seviyelere sahip eksipiyanların seçimi, ilaç ürününün performansı için kritiktir.

Formülasyonların elde edilen çıktılarındaki varyasyonu gözlemlemek için deneysel bir tasarım çalışması yapıldı ve karmaşık ilişkileri modelleyerek optimizasyona izin veren Modde Pro 12.1 istatistiksel bilgisayar programı kullanılarak değerlendirildi.

Bulgular ve sonuçlar: Yapılan çalışma sonucunda optimal formilasyonun dolgu maddesi MicroceLac® 100 ve lubrikant maddesi ise %0,22 Magnezyum Stearat içerdiği ortaya kondu.

Bu çalışma, formülasyondaki eksipiyanların etkisinin daha iyi anlaşılmasına, formüle edilmesine ve farklı formülasyonların geliştitilmesine yardımcı olur.

Anahtar kelimeler: Compaction Simulator, Co-processed filler, Ibuprofen DC 85W, Lubrikantlar**,** Quality by Design.

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SUMMARY

Aim: The objective of this study was to apply quality by design (QbD) principles for formulation development and to define the desired product quality profile (QTPP) and critical product quality characteristics (CQA). Compaction simulator was used in order to characterize the deformation behaviour and compaction properties of two co-processed lactose-based fillers, as well as to determine the efficiency of lubricant type and concentration in formulations.

Materials and Method: Ibuprofen DC 85W, a pre-granulated direct compression product containing 85% of Ibuprofen and 15% of excipients, was chosen for this study. Cellactose® 80 and MicroceLac® 100 were used as filler and Magnesium Stearate, Stearic Acid and Sodium Stearyl Fumurate were used as lubricants.

QbD approach is used to enhance understanding of how critical quality attributes contribute to the overall quality of the drug product by adding various formulation parameters to the filler and lubricants.

As commonly known, the product development stage is quite complex, requires intensive knowledge and is time consuming. The selection of excipients with the correct functionality and their corresponding levels in the formulation of the drug product are critical to the performance of the drug product.

An experimental design study was performed to observe variation in the formulations' obtained outputs and evaluated using Modde Pro 12.1 statistical computer program that allows the optimization by modelling complex relationships.

Findings and Results: The results of optimum formulation revealed MicroceLac® 100 as the superior filler as well as Magnesium Stearate at 0.22% as the optimum lubricant.

This study enriches the understanding of the effect of excipients in formulation and assists in improved formulation design.

Keywords: Compaction Simulator, Co-processed filler, Ibuprofen DC 85W, Lubricants**,** Quality by Design.

CHAPTER ONE

INTRODUCTION AND AIM

1.1 Quality by Design

Quality by Design (QbD) is characterized as a systematic and scientific risk-based approach to the production of pharmaceutical products and processes that targets consistent performance/quality of drug products and subsequently cost reduction as a major result. As commonly known, the product development stage is quite complex, requires intensive knowledge and is time-consuming. In this process, multivariate interactions are involved between raw materials and process conditions. For the processability and consistency of the finished product, these interactions are very critical (Aksu et al., 2013).

The modeling of Ibuprofen tablet formulation and production using modern science and risk-based techniques has many advantages over conventional modelling techniques, especially in the assessment of nonlinear relationships, which are frequently observed in pharmaceutical operations. QbD approach is used to enhance the understanding of how the critical quality attributes relate to the overall quality of the drug product by applying various formulation parameters to the filler and lubricants (Aksu et al., 2013).

Following a QbD approach will result in an increased level of drug product consistency and minimize uncertainty (Chudiwal et al., 2018). The most important aspect of QbD is to be aware of the effect of processes and formulation parameters on the characteristics of the product and to optimize these parameters according to the final required specifications (Lawrence, 2008).

Several QbD related studies have studied the influence of excipients on the performance of drug products, either by changes in the amount of excipients in the formulation or through the use of alternative excipients. The selection of appropriate functional excipients and their corresponding levels in the formulation of the drug product is critical to the performance of the drug product. (Kushner et al., 2014).

1.2 Solid dosage forms

Generally, the oral route of administration is considered to be the most common and applicable way of administration for most therapeutic agents producing systemic effects in the pharmaceutical industry, owing to its several advantages and high patient compliance compared to many other routes (Hirani et al., 2009; Valleri et al., 2004). Currently, more than 80% of all dosage forms on the market are comprised of tablets because they (i) offer dosage accuracy, (ii)present lower likelihood of toxicity compared to parenteral dosage forms due to their reduced bioavailability, (iii) are easy to dispense, (iv) offer better stability to heat and moisture compared to liquid and semi-solid formulations, and (v) are tamper resistant compared to capsules (Jivraj et al., 2000).

To begin with, tablets are solid dosage forms, that usually consist of the active pharmaceutical ingredient (API) combined with the aid of suitable pharmaceutical excipients, that could be available in several forms (powder, crystalline or granular), which in turn may or may not include diluents depending on the drug used (Taylor & Aulton, 2013).

The choice of excipients is a critical issue since, the final product primary features will be established and the physical form, texture, stability, taste and the overall appearance will be contributed (Tyagi et al., 2017).

The selection of appropriate functional excipients and their corresponding levels in the formulation of the drug product is critical to the performance of the drug product. (Kushner et al., 2014).

1.3 Aim and Scope

1.3.1 Research objective

The aim of this PhD thesis is the application of Quality by design (QbD) approach to development and optimization of Ibuprofen tablets. The relationships between the formulation properties and desired product properties which are defined as critical for product quality were investigated.

The study evaluated compaction produced by a single punch compaction simulator in order to characterize the deformation behaviour and compaction

properties of two co-processed lactose-based fillers, as well as to determine the efficiency of lubricant type and concentration in formulations. This research enriches the understanding of the effect of excipients in formulation and assists in improved formulation design.

1.3.2 Work plan

1. Powder characterization of excipients used in the formulation.
    1.1 True density, morphological studies and flowability studies for Ibuprofen and co-processed lactose-based fillers.
2. Study design determined
    2.2 Determine QTPP for Ibuprofen tablet formulations
    2.3 Formulation Design
3. Formation of Compacts
    3.1 Using a compaction simulator to press formulations at different pressures (50MPa- 150MPa)
    3.2 Formulations for combination of Ibuprofen, lactose based fillers and lubricants.
4. Compact characterization
    Evaluation and comparison of post-compression parameters
5. Use of QbD approach for Data Analysis using Modde Pro 12.1 statistical computer program that allows the optimization by 5odelling complex relationships to obtain design space and optimized formulations.
6. Analytical study & Assay for Ibuprofen Optimized Formulations

CHAPTER TWO
GENERAL INFORMATION

2.1 Ibuprofen

2.1.1 Indication of Ibuprofen

Ibuprofen is the chemical relative of a group of substituted phenylalkanoic acids and is a 2-phenylpropionic acid. As an anti-inflammatory drug in humans, it was launched in England in 1967 and in the United States in 1974. Ibuprofen is a derivative of chiral propionic acid that belongs to the non-steroidal anti-inflammatory drug class (NSAIDs). It is used in the treatment of inflammatory disorders such as rheumatoid arthritis, osteoarthritis, ankylosing spondyolitis, mild and moderate pain, dysmenorrhoea, vascular headache and fever because of its analgesic, antipyretic and anti-inflammatory behavior. (BASF, 2019)

2.1.2 IUPAC name, chemical formula and structure

IUPAC name: 2-[4-(2-methylpropyl)phenyl]propanoic acid

Chemical Formula: C13H18O2

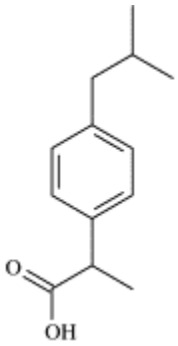


Figure 2.1 Chemical structure of Ibuprofen (Winkler et al. 2001).

2.1.3 Pharmacology

The mode of action is believed to involve the reversible inhibition of the enzyme cyclooxygenase (COX) which is responsible for the biosynthesis of prostaglandins (PGs) from arachidonic acid in the cellular membrane. In the different tissues, prostaglandins are distributed and have, among other properties, a powerful effect on the smooth muscles. PGs are synthesized in increased concentrations in the event of an inflammatory stimulus or blood flow disruption and sensitize the tissues to the action of other chemicals, such as histamine and kinins. Symptoms such as pain and inflammation appear as a result. Fever occurs by the influence of the PGs on the heat regulation centre in the hypothalamus. There, the natural body temperature is increased to 37 ° C. Also, the most likely cause of gastrointestinal side effects is the inhibitory action of NSAIDs on PG synthesis. For physiological functions, PGs play an important role, such as synthesizing protective alkaline secretion in cells of the gastric mucosa. PG synthesis inhibition can lead to decreased defense of the gastric mucosa which can lead to infection, abdominal pain and ulcers. Ibuprofen has the best risk profile benefits and the lowest rate of severe gastrointestinal adverse effects for NSAIDs. (BASF, 2019).

2.1.4 Physicochemical properties

Polymorphism and crystallinity are considered among the prime determinants through which the optimization of drug substances is mandatory in the development of a stable, effective, safe, and reproducible dosage form. Different polymorphs have differences in their hydrogen bonding, dissolution rate, density, melting point, stability, and packing energy (Huskisson et al., 1971). The phenomenon of polymorphism is studied in context of physical stability of dosage forms.

As more than one polymorphic structure, several crystalline organic compounds may occur. The transformation may be a solid state chemical reaction if the molecules of such a compound assume a different relative geometry by breaking old or creating new bond associations during the transformation from one polymorph

to another. Accordingly, the reactant polymorph and product polymorph might exhibit very different chemical behavior (Szczeklik et al., 1976). The crystallinity of a solid drug product is of major importance and has a multifaceted effect on the efficiency of a drug's dosage type in many respects. In addition, the degree of crystallinity has been found to correlate strongly with the formulation's stability and acceptability (Bach et al., 1977; Phillips & Muirden, 1972; Tokumitsu et al., 1977), and crystalline compounds are more chemically stable than their amorphous or glass counterparts (Kantor, 1979; Meacock & Kitchen, 1976).

It is necessary to critically evaluate the drug from the crystallinity point of view to avoid batch-to-batch variation of crystal form that otherwise results in bioequivalent dosage forms. All of these properties can have a tremendous impact on the performance of a solid dosage form and ultimately the success or failure of a pharmaceutical product (Kantor, 1979).

2.1.5 Pharmacokinetics of Ibuprofen

Ibuprofen is readily absorbed by mouth and does not seem to accumulate in tissues that are not in equilibrium with the plasma. The peak plasma levels are reached within 1 – 2 h. After an oral dose of 200 – 400 mg, 15 – 25 mg/ml appear in the blood serum (BASF, 2019). Plasma half-life of the drug is between 1 and 3 h in humans, and in a comparison of normal and adjuvant arthritic rats the half-life was the same for the two groups. It has two metabolites, both pharmacologically inactive, and urinary excretion of a single dose of the drug and its metabolites is complete in 24 h (Kantor, 1979)

2.1.6 Powder Characteristics

Ibuprofen exhibits a poor flowability and compressibility due to its viscoelasticity and high cohesivity (Nokhodchi et al., 2015; Rasenack & Muller, 2002). In addition, ibuprofen shows a high tendency to stick to tablet instruments, owing to its low melting point of 75-78 °C (Rasenack & Muller, 2002; Saniocki

Sakmann & Leopold, 2012). During tableting, localised high temperature spots can occur and result in a partial melting of ibuprofen. The subsequent rapid recrystallization of ibuprofen is assumed to cause the sticking to the tablet tooling (Alkarawi et al., 2018; Bechard & Down, 1992; Roberts et al., 2004).

As a consequence, ibuprofen powder formulations often have to be granulated (Jbilou et al., 1999; Rasenack & Muller, 2002) although direct compaction is generally the more preferred production method to achieve high economic efficiency (Bolhuis & Armstrong, 2006; Rasenack & Muller, 2002). However, because of the poor compressibility of ibuprofen, one limitation of the direct compaction process is the drug content of the tablet formulation, which is often limited to approximately 30% (Alkarawi et al. 2018; Jivraj et al. 2000).

Several attempts have been made to enhance ibuprofen's tableting behavior during direct compaction with respect to powder formulation, such as optimization of formulation (Bushra et al., 2008; Roberts et al. 2003), crystal engineering, selection of the optimal grade of ibuprofen (Saniocki Sakmann & Leopold, 2012), or the implementation of optimal storage conditions. The nanocoating of ibuprofen powder particles with different excipients such as magnesium stearate (Qu et al., 2015) or fumed silica is another promising approach that has been subject to recent investigations (Zhou et al., 2013). Improvements in powder flowability and tabletability have been made in both situations. In these studies, however, the sticking tendency was not investigated. A directly compressible grade of ibuprofen, which contains 85 percent ibuprofen, was developed particularly to address sticking and tabletability problems with ibuprofen. Ibuprofen DC 85 W granules are produced by roller compaction followed by nano-coating of the fumed silica granules (Meyer-Boehm et al. 2014). Compared with other grades, the tableting and anti-sticking properties of Ibuprofen DC 85 W were reported to be superior (Alkarawi et al. 2018; Meyer-Boehm & Eining, 2006).

2.2 Solid Dosage Forms

Generally, the oral route of administration is considered to be the most common and applicable way of administration for most therapeutic agents producing systemic effects in the pharmaceutical industry, owing to its several advantages and

high patient compliance compared to many other routes (Hirani et al., 2009; Valleri et al., 2004). Currently, more than 80% of all dosage forms on the market are comprised of tablets because they (i) offer better stability to heat and moisture compared to liquid and semi-solid formulations, (ii) present lower likelihood of toxicity compared to parenteral dosage forms due to their reduced bioavailability, (iii)offer dosage accuracy, (iv) are tamper resistant compared to capsules, and (v) are easy to dispense (Jivraj et al., 2000).

There are a variety of forms in which the solid medicaments can be administered orally. These include: tablets, capsules, pills, powders etc. Tablets of various kinds and hard gelatin capsules comprise a major portion of drug delivery systems that are currently available (Allen & Ansel, 2013; Hirani et al., 2009).

2.2.1 Pharmaceutical powders

A powder is defined as a heterogeneous mixture of solid particles as well as air existing both inside and outside of the particles (Nyström 1993). Powders have complex rheological behavior with the physical properties of solids, liquids and gases. Mixtures of an active pharmaceutical ingredient and a variety of excipients are typically pharmaceutical powders. The majority of pharmaceutical powders consist of highly crystalline particles with no uniform particle shape and size distribution (York 1973).

2.2.2 Tablets

To begin with, tablets are solid dosage forms, that usually consist of the active pharmaceutical ingredient (API) combined with the aid of suitable pharmaceutical excipients, that could be available in several forms (powder, crystalline or granular), which in turn may or may not include diluents depending on the drug used (Taylor & Aulton, 2013). They resemble a solid, biconvex or flat shaped, which in turn have diversity in the size, shape and weight depending on the medicaments used for preparation. Moreover, variation in the hardness, disintegration, dissolution

characteristics and thickness is also observed which is highly dependent on their intended use and method of manufacture. There are two ways to manufacture tablets, compression and molding, in which compression resembles the dominant method on the large scale of production (Allen & Ansel, 2013).

Briefly, there are several reasons behind the tablets popularity: Primarily since it is administered orally, this provides a safe and convenient way of administration. Secondly, compared to liquid dosage forms, tablets (and other solid dosage forms) are considered to be more physically, chemically and microbiologically stable. Thirdly, accurate dosing of the drug is achieved due to the preparation procedure (Hirani et al., 2009). Fourthly, the handling of such dosage forms are quite convenient. Finally, the mass production of tablets can be relatively cheap along with robust and quality-controlled production procedures that results in an elegant preparation of consistent quality (Allen & Ansel, 2013).

On the other hand, such dosage forms encompass certain drawbacks. For instance, patients who are unconscious, children, elderly, mentally retarded or patients that have problems in swallowing would face difficulties. Nevertheless, one of the most important challenges in such dosage forms, is in formulating poorly water soluble, amorphous or even hygroscopic drugs, which in turn results in poor bioavailability. Additionally, the cost of production may increase if coating or encapsulation is applied to the drug (Bhuyian et al., 2013).

Shapes of tablets are carefully considered within specific parameters to be acceptable by patients. Tablets take the forms of several shapes including round, oblong, cylindrical, oval, triangle, with the option to be scored or grooved for ease of breaking into two halves or more for enhancing patient's ease of swallowing and ensure that the dose is accurately administered.

Tablets can be of several types depending on their intended use and method of manufacture. In the framework of intended use, tablets can either be immediate release or controlled release tablets. Immediate release tablets are required in conventional therapy to provide immediate onset of actions, such as pain relieve medications. They tend to release ≥85% of labeled amount within 30 minutes (Nyol & Gupta, 2013)

2.2.3 Tablet Manufacturing Methods

The manufacturing of compressed tablet dosage forms which are prepared from powders can be done by direct compression, wet granulation or dry granulation (Allen and Ansel, 2013). Wet granulation (WG), dry granulation (DG), direct compression (DC), and extrusion/spheronization (SP) are processes used to prepare a blend of the active pharmaceutical ingredient (API) and the excipient(s) prior to converting into a tablet or capsule dosage form (Allen and Ansel, 2005; Hedden et al., 2006)

Direct compression is a simple and cost-effective method of directly making compacts from a powder blend of API and excipients.

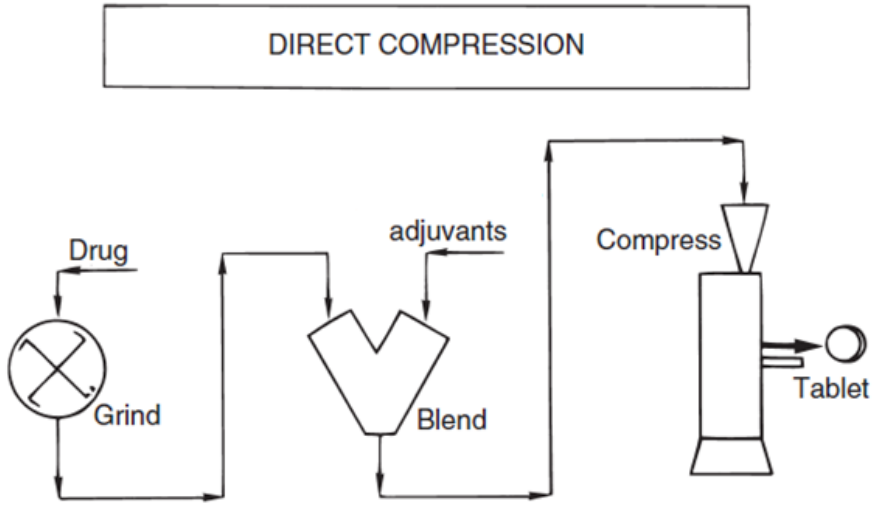


Figure 2.2 Direct Compression method for tablet preparation (Allen and Ansel, 2005)

The API is combined with a wet binder (often starch) and other excipients in wet granulation and then passed sequentially through sieves to obtain granules suitable for tableting (Allen et al., 2000). The most common technique for tableting is wet granulation, as it allows a large number of drugs to be compacted at a wide variety of doses. Nevertheless, when wet granulation is used, it may be difficult to achieve batch to batch reproducibility, particularly when using a highly soluble API. In such cases, during drying, the API may migrate from the core to the surface. In addition, during unit operations, such as blender-to-bin transfer, and bin-to-tablet press transfer, segregation may occur. The uniformity of the dosage may be influenced by such

segregation. In direct compression, this issue may also be present if there is a significant difference between powder mixture densities (Hedden et al., 2006).

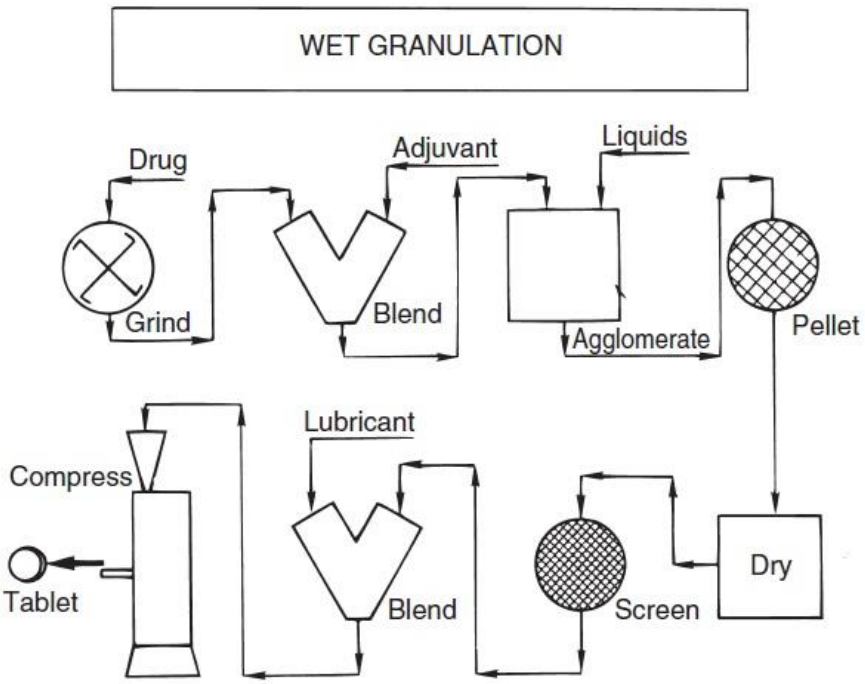


Figure 2.3 Wet Granulation method for tablet preparation (Allen and Ansel, 2005)

The method of dry granulation involves the preparation of a dry mixture of API and excipients, followed by pre-compression of powder with high-pressure rollers using 1 to 6 tons of force to form ribbons (roller compaction) which are then milled and sized. A dry binder and/or a lubricant are added if necessary and the blend is compressed into a tablet.

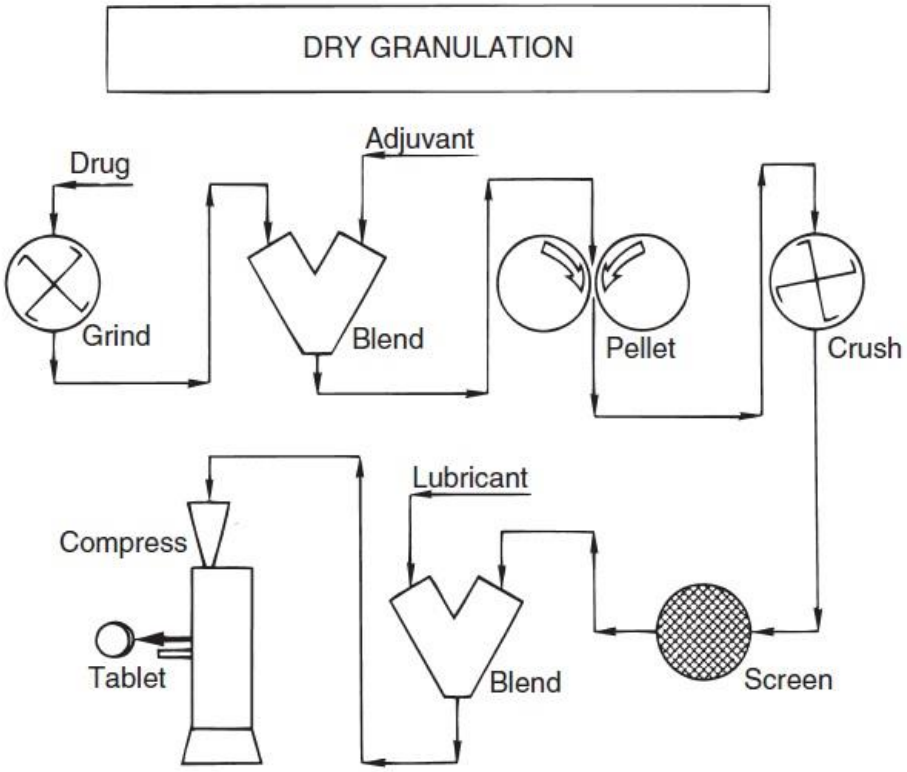


Figure 2.4 Dry granulation method for tablet preparation (Allen and Ansel, 2005)

The API is blended with the excipients in the extrusion/spheronization process, followed by the addition of a wetting agent or binder in an appropriate liquid liquid (water or ethanol). The plastic mass resulting from this is extruded to form a noodle-like extrudate. The extrudate is then converted to beads with a spheronizer. If required, the beads are dried and coated before placing them in capsules or making tablets. (Soh et al., 2008).

2.2.3.1 Direct Compression

As the term implies, direct compression requires compressing the tablets raw materials directly after they have been mixed efficiently. Apart from blending the active pharmaceutical ingredient with excipients, nowadays the pharmaceutical industries use this concept in tablet production (Gibson, 2016).

Mainly direct compression is most suitably applied to two common

formulation cases. Initially, it is applied to drugs that are relatively soluble, were they could be processed as coarse particles to ensure good flowability and secondly, using the little amount of potent drugs were they can be mixed with coarse excipients (Taylor & Aulton, 2013).

An important tip to highlight is that, the raw materials being compressed should have good flowability in order to flow uniformly in the die cavity and form a firm compact. In addition, the raw materials should be considered as directly compressible meaning that they should have good compaction properties. Therefore, the reasons behind the universal applicability of this method are the introduction of formulation excipients that are capable of providing the required compressible characteristics and the utilization of force-feeding devices in order to improve the flowability of the powder blends. Now depending on the amount of the active pharmaceutical ingredient placed in the formulation, for tablets that constitute a major portion of the tablet weight, it is essential that the drug should possess the physical features needed for directly compressible formulations. On the other hand, if the drug substance constitutes less than 25% of the final tablet weight then it is necessary to find a suitable filler or diluent that has directly compressible features implemented (Felton, 2013).

2.2.3.1.1 Advantages of Direct Compression

1. Provides an economical simple way of production, since there are fewer steps included and therefore savings can occur in many areas.

2. Have the ability to do the process in the absence of heat and moisture and also no need to expose the powder mixture to high compaction pressures. Therefore, preventing any stability issues.

3. Can positively alter the dissolution rate for many drugs by increasing the disintegration of the tablet and the disintegrant would be able to function optimally (Iqubal et al, 2014).

2.2.3.1.2 Disadvantages of Direct Compression

1. The costs involving raw materials and raw material testing are known to be high, since the success or failure of the directly compressible formulation is mainly governed by the choice of excipients, especially the filler-binder.

2. The probability of having poor content uniformity in the final dosage form is quite evident in the direct compression process.

3. It is quite important to select the suitable lubricant in terms of type and amount during direct compression process, to avoid bioavailability problems. (Lieberman et al., 1989)

Since material properties are not altered by previous process steps, DC is dire ctly affected by these properties. Therefore, direct compression from the starting ingredients, including excipients, requires increased efficiency, quality and consistency.

Excipients play a significant and often crucial role in the quality of drug prod ucts. (Thoorens et al., 2014)

The material characteristics, such as flowability, compressibility and dilution potential, are highly influenced by direct compression, since ~70 percent of commercial formulations contain excipients at higher fractions than APIs. Thus, an optimal DC excipient allows one to prepare API compacts even at levels below 50 percent excipient (Jacob et al., 2007).

2.3 Formulation Excipients

According to the International Pharmaceutical Excipient Council, an excipient is defined as “Any substance other than active drug or pro-drug that is included in the manufacturing process or is contained in finished pharmaceutical dosage forms” (Chaudhari & Patil, 2012).

For making solid dosage forms, there is a wide range of excipients that can be used. Based on their chemical nature, inorganic (such as dicalcium phosphate), synthetic (such as polyvinylpyrrolidone) and semisynthetic (such as hydroxypropyl cellulose) excipients can be classified as natural (such as cellulose, starch, chitosan,

etc.).

The choice of such excipients is a critical issue since, the final product primary features will be established and the physical form, texture, stability, taste and the overall appearance will be contributed (Tyagi et al., 2017).

Even excipient grade selection can cause problems in DC. Selecting an improper grade of excipient could lead to segregation and higher sensitivity to lubricants (Almaya and Aburub, 2008).

The following characteristics should be present in the pharmaceutical excipient for it to be considered as an ideal excipient. Initially, they should be physiologically inert and physically and chemically stable. Moreover, they should be pyrogen-free and do not have any interference with the drug's bioavailability. Last but not least, they should confirm to all currently applied regulatory obligations and be relatively economical and non-expensive (Chaudhari & Patil, 2012; Lieberman et al., 1989).

Generally, excipients are classified into two major categories. Primarily, additives that affect the pharmaceutical dosage form compressional characteristics and these include fillers, binders, lubricants, glidants and anti-adherents. Whereas, there are additives that mainly provide additional desirable characteristics to the final product such as disintegrants, flavorings, sweeteners, sorbents, surfactants, colorings and preservatives (Chaudhari & Patil, 2012; Lieberman et al., 1989; Patel et al., 2011).

In spite of excipients being classified according to their primary functions, there are several excipients that are considered to be multifunctional. A multifunctional excipient is defined as a material that has more than one functional property. Functionality describes the activity of an excipient. For instance, the same excipient may act differently when present at different concentrations (Patel et al., 2011).

2.3.1 Functional Excipients for Tablets

A binder, filler, glidant (flow enhancer), disintegrant and lubricant are generally involved in the manufacture of a tablet dosage form. A glidant enhances the powder mixture's flowability; a lubricant is added to reduce the friction between the powder and the tooling of the tablet. The latter also improves the efficiency of tablets

and reduces punch-and-die wear. The filler (diluent) is used to increase the bulk to the desired size/volume of the tablet or capsule, easing compact handling and administration. A binder provides sufficient tensile strength for the forming of granules or tablets, while the use of a disintegrant enables the tablet to split into particles when it comes into contact with water. In response to the pressure applied, compressibility is expressed as the relative volume reduction of the powder bed, and compactibility is the ability to form a compact with sufficient strength when applying a compression force (Allen et al., 2000).

2.3.1.1 Diluents/ Filler

To increase the volume/weight of the dosage form, diluents are added into tablet or capsule dosage forms and as such, they may also be referred to as fillers (Thoorens et al., 2014). They also enhance the cohesion, flow and allow direct compression manufacturing.

There are several types of fillers, but in order to be classified as directly compressible filler, it should have good compaction and flow properties, high capacity, possess appropriate particle size distribution, have high bulk density and able to be produced reproducibly (Lieberman et al., 1989).

Diluents are thus used, usually from 5 to 80% of the weight of the tablet (Lachman et al., 1986). They are added to formulations to increase compact bulkiness, but they are sometimes added to enhance cohesion, enable compression, improve flow, and adjust tablet weight (Swarbrick and Boylan, 1986).

The compressibility of the API influences the dilution capacity of an excipient. It refers to the quantity of excipient integrated with a drug, without sacrificing its functional properties, such as compactibility or compressibility, with a medication (Allen et al., 2000).

Loading ability or dilution potential is known as the minimum excipient quantity that does not alter its compressibility, flow rate and capacity to shape hard compacts at low pressures when mixed with a drug (Flores et al., 2000).

2.3.1.1.1 Use of Lactose in tablet formulations

In direct compression tablets, lactose is one of the most used filler/binder excipient. Hydrous and anhydrous crystalline forms of alpha-lactose, β-lactose anhydrate, and amorphous lactose are commercially available forms of lactose (Lerk 1993). In stable or unstable form, the alpha-lactose anhydrate may exist. The unstable form is highly hygroscopic and can be produced at temperatures of 100-130 °C when alpha-lactose hydrate is heated. With the heating temperature above 130 °C, the non-hygroscopic stable form can be manufactured. Only in anhydrous form can β-lactose occur, since no water is introduced into the crystal lattice during the crystallization process. The spray-dried lactose form includes monohydrate or anhydrate of crystalline lactose and the amorphous lactose form (Vromans et al. 1986).

There are various compaction properties of the various types of lactose (Bolhuis and Zuurman, 1995). It is recognized that crystalline lactose consolidates mainly through the brittle fracture because the degree of plastic deformation is very limited (Vromans et al 1985). Plastic flow has been shown to distort the amorphous lactose (Vromans et al. 1987).

The compactability of the alpha-lactose monohydrate depends on the powder surface area prior to compaction, since the binding potential increases with increasing surface area (De Boer et al. 1986). As the degree of fragmentation during the compaction rises, the binding surface rises. Different fractions of the-lactose monohydrate particle size have different compactability profiles. For smaller median particle size fractions of lactose, the compactibility is higher. The ground and sieved alpha-lactose monohydrate grades used for tablet compression usually compromise the properties of flow and compression (Bolhuis and Zuurman, 1995).

The β-lactose anhydrous fragments are higher than the -lactose fragments. It has greater compactability because of the more spherical particle form and the rougher particle surface (Vromans 1987). The available types of β-lactose are not pure substances, but contain around 15% of the alpha-lactose monohydrate or anhydrate, so both components make up the compression actions (Bolhuis and Zuurman 1995).
Spray-dried lactose is the best candidate used as direct compression filler. This is mainly because, it exhibits greater flowability and compressibility features (Gohel & Jogani, 2005; Rowe et al., 2006).

2.3.1.1.2 Use of Cellulose in tablet formulations

The most abundant natural linear polymer consisting of 1,4-linked-β-D-glucose repeat units is cellulose and is known to exist in the following separate allomorphs: I(from algae), I(from superior plants), II (the most stable form formed by mercerization), IIII and IIIII (from ammonia at -30°C), and IVI and IVIII (from ammonia at -30°C) (produced at 260°C in glycerol). In its physicochemical properties, each allomorph differs (Klemm et al., 1998a; Klemm et al., 1998b). Cellulose III is produced when native cellulose is handled at low temperatures with liquid ammonia, while cellulose IV is obtained at high temperatures by treating regenerated cellulose (Figure I-4) (Krassig, 1996). Of these, the most common form is the cellulose I (CI) allomorph, and the most stable form is cellulose II (Kroon-Batenburg et al., 1996). It is possible to convert CI to CII but not vice versa (Blackwell and Kolpak, 1975; Kolpak and Blackwell, 1976). The chain orientation is thus exclusively parallel (Krassig, 1996), as shown in Figure I-5, in cellulose I (CI), while the chains are organized in an anti-parallel manner in cellulose II (CII).

The cellulose-I lattice comprises microcrystalline cellulose (MCC). It is obtained from wood pulp and cotton linter by treatment at boiling temperatures with dilute strong mineral acid (HCl) up to the degree of polymerization-off stages (Battista et al., 1957; Battista and Smith, 1961). Acid hydrolyses the polymer chains' less ordered regions, leaving the crystalline regions intact. MCC powder is also called hydrocellulose or hydrolyzed cellulose.

Due to its excellent diluent and binding properties and low moisture content, microcrystalline cellulose I (MCCI) has been the dominant excipient used for direct compression since the 1970s. The strong binding properties of MCC are due to the bonding of hydrogen between cellulose particles that deform plastically. It suffers, however, from lubricant sensitivity and poor flow (Lerk et al., 1974; Moreton, 1996).

2.3.1.1.3 Spray-dried lactose

Spray-dried lactose is one of the universally used lactose forms. Guncel and Lachman were the first individuals to describe the spray-dried lactose process, according to Gohel and Jogani (2005:82). The method of spray drying is not common to many individuals. In the early 1960s, spray-dried lactose appeared and was the first product specially formulated for direct compression (Takeuchi et al., 1998). In short, spray drying is a technique in which various solutions are easily dried in a heated chamber by atomizing the liquid until it reaches a particulate form. Dry solvent-based systems can also be sprayed under controlled conditions. (Takeuchi et al., 1998).

During the spray-dry method, there are a few standard unit operations. The pre-concentration of the liquid starts with this procedure; evaporation was previously used but is currently too costly. The next step is atomization, which primarily consists of the formation of droplets. In the industry, a few atomization techniques are used, such as pressure nozzle atomization, atomization of two-fluid nozzles and centrifugal atomization. All of the methods mentioned give a relatively good average control of particle size. If you compare the approaches, the particle distribution varies a lot. During the spray-dry process, this step is the most critical step.

During spray drying, the third major step consists of drying the droplets in a stream of hot, dry gas, generally air. It follows the separation of powder from moist gas, where the process is completed by cooling and the packaging of the product. The cyclone spray dryer is one of the most commonly used spray-dryers. In short, a concentrate of the liquid product is pumped into the atomizing device where tiny droplets are formed. A stream of hot gas reaches these droplets and, when in dry air, causes them to lose moisture quickly. Through centrifugal action, the dry powder is then separated from the moist air. Finally, the atomizer involves either a rotating disk with a 2000-20,000 rpm rotation or static high-speed jet nozzles (Broadhead, et al., 1992).

A bright option for improving the functionality of excipients in a tablet formula is new combinations of existing excipients. There are many possible combinations that will contribute to the desired performance characteristics, but because of the possibility that one excipient might interfere with the properties and functions of the other excipients, this is a very complex process.

2.3.1.1.4 Co-processed excipients

Co-processing is described as a combination of two or more established excipients by a pharmaceutical process. The products formed are physically altered in such a way that their stability and chemical structure are not lost. This signifies that excipients preserve their individual chemical properties, while increasing their functional efficiency synergistically.

A co-processed material typically has superior characteristics than the physical combination of individual components (Rojas et al., 2012). For co-processing, a mixture of a plastic and a brittle deforming material is preferable.

Co-processing dates back to the late 1980s, when it emerged as the first co-processed excipient. In the 1990s, Cellactose®, a mixture of powdered cellulose and lactose, was the second excipient identified after co-processed microcrystalline cellulose and calcium carbonate (Nachaegari & Bansel, 2004). Starlac®, a combination of maize starch and spray-dried lactose, is one of the recent co-processed excipients on the market. All these co-processed excipients need to be developed on a sub- particle level where particle engineering takes place.

Particle engineering is a very broad concept that involves the manipulation of particle parameters such as shape, size, and size distribution; and changes the polytypic and polymorphic parameters on a molecular level. All of the above mentioned parameters are translated into bulk-level changes such as flow properties, compression, moisture sensitivity and the ability to use a machine. A more understandable explanation for co-processing is that the process is based on a novel concept of two or more excipients, interacting on a sub- particle level to provide a synergy of functional improvements and the masking of the undesirable properties of each individual excipient (Nachaegari & Bansel, 2004).

Before any co-processing can take place, it is important to keep the individual materials‟ characteristics in mind. Many materials appear to show a superior reaction to other materials. In general, the co-processing of two or more individual excipients is a mixture of a fragile substance such as lactose (75%) and a synthetic excipient such as cellulose (25%) to obtain Cellactose®. A significant parameter for the acquisition

of specific properties is the ratio in which these products are used. The proportion of brittle and plastic materials used in this particular case prevents the conservation of elastic energy during compression. In order to achieve optimal performance, there are also extreme instances where the ratio changes significantly. The truth remains that materials with plastic deformation and brittle fragmentation must be used (Nachaegari & Bansel, 2004).

Cellactose® 80 and MicroceLac® 100 are spray-dried lactose based co-processed excipients used in direct compression. Cellactose® 80 is composed of 75% α-lactose monohydrate and 25% powder cellulose, and MicroceLac100 is composed of 25% microcrystalline cellulose (MCC) and 75% α-lactose monohydrate.

It is known that lactose has a brittle deforming behavior, while cellulose derivatives a re seen to deform more plastically (Al-Ibraheemi et al., 2013). The compactibility is attributed to a synergetic effect of consolidation by fragmentation of lactose and plastic deformation of cellulose (Garr & Rubinstein, 1991; Gohel & Jogani, 2005).

This combination prevents too much elastic energy from being retained during compression, which is attributed to the compacts tendency for capping and lamination (Dudhat et al., 2017; Gupta et al. 2006). Table 2.1 below, shows features of Cellactose® 80 and MicroceLac® 100

Table 2.1 Co-processed, spray dried lactose-based fillers (Camargo, 2011).

Excipient	Principle features
Cellactose 80 (Lactose-Cellulose)	• Has good compactibility attributed to the synergic effect of consolidation by fragmentation of lactose and the plastic de formation of cellulose (Arida and Al-Tabukha, 2008). • During spray drying, lactose particles coat the cellulose fibers. Lactose renders good flow and solubility whereas cellulose contributes to particle binding (Belda and Mielck, 1996). • Produces stronger compacts than the physical mixture of 75% cellulose and 25% lactose. Compacts made at 150 MPa have a hardness of 140N (Schwarz et al., 2006). • Disintegration of its particles starts once the outer lactose shell has dissolved allowing access towards the cellulose core (Casalderrey et al, 2004). • At low compression pressures fragmentation predominates, and at higher than 180 MPa plastic deformation is prevalent. It is also more compactable than lactose (Schmidt and Rubensdörfer, 1994). • Compactibility is affected by high compression speeds (Arida and Al-Tabakha, 2008).
MicroceLac 100 (Lactose-MCC)	• It has superior flowability and binding properties compared to the mixture physical of MCC and different lactose grades (Schwarz et al, 2006, Clerch, 2008). • It forms stronger compacts with faster disintegration times than those of Cellactose 80(Muzikova and Novakova, 2007).

2.3.2.2 Lubricants

Lubricants are a minor but essential formulation component for solid dosage forms. Technically, they minimize wear of punches and dies thus preserving tooling by reducing die-wall friction, in addition to preventing fill material from sticking to the punches and dies (Paul and Sun, 2018; Wang et al., 2004). These excipients mainly prevent the adhesion of tablets to the punches and dies during manufacture by reducing the inter-particulate friction and therefore facilitate the ejection of the tablet from the die cavity.

One of the most complex and challenging aspects of tablet formulation has always been lubrication. If anything, the lubrication of direct compression powder mixtures is more complex than that of traditional granulation. In general, there are two categories of problems associated with lubricating direct compression mixtures: (1)

the type and quantity needed to produce adequate lubrication and (2) the softening effects resulting from lubrication (Sheth et al., 1980), owing to the lubricant particles coating the larger excipient particles and interrupting interparticulate bonding (Velasco et al., 1997).

Properties of the compact critical to its performance include the tablet hardness, ejection force,
disintegration, and dissolution.

It is widely acknowledged that these properties are influenced by lubricant. The extent to which the lubricant modifies these properties is a function of type and concentration of the lubricant (Louw, 2003).

Lubricants are intended to hinder components from aggregating together, and lower attrition between die wall at the time tablet eject. Lubrication in fact is a part of the coating process, and in order to increase lubrication efficiency, lubricant particles are preferred to be small.

Lubricant can adversely affect the quality of production, whilst the primary purpose of lubrication is to increase the efficiency of manufacturing. For instance, continued lubrication mixing time, can lead to obstruction of the dissolution process, making the tablet feebler. Examples on lubricants: (talc, stearin like magnesium stearate, high molecular weight PEG, waxes) (Wang et al., 2010).

2.3.2.2.1 Classification of lubricants

By two mechanisms, lubrication is considered to occur. The first is called fluid (or hydrodynamic) lubrication, since a finite and continuous layer of fluid lubricant is assumed to distinguish the two moving surfaces. An example of a fluid-type lubricant is a hydrocarbon such as mineral oil, although a weak lubricant. Hydrocarbon oils do not readily allow the application of tablet granulations and will produce tablets with oil spats unless atomized or applied as a fine dispersion. The second process, boundary lubrication, results from the adherence to the metal surfaces of the die wall of the polar portions of molecules with long carbon chains. An example of a boundary lubricant is Magnesium Stearate. Boundary-type lubricants are better than fluid-type lubricants because the adherence of a boundary lubricant to the die wall is greater than that of the

fluid type. As the polar end of the boundary lubricant should bind to the oxide metal surface more tenaciously than the non-polar fluid form, this is to be expected (Banker et al., 1980).

Lubricants can be further listed according to the solubility of their water (as water-soluble or water-insoluble). The choice of a lubricant may depend in part upon the mode of administration and the type of tablet being produced, the lubrication and flow problems and requirements of the formulation, drug compatibility considerations, cost, various physical properties of the powder system being compressed, and the dissolution and disintegration properties desired, (Banker et al., 1980).

a) Water-insoluble lubricants

Some of the more common anti-frictional agents encountered in direct compression are hydrophobic and consequently might affect the release of the drug. In practice this is often markedly so, and for this reason it cannot be overemphasized that lubricant concentration and mixing time should be kept to the absolute minimum. They may also significantly reduce the mechanical strength of the tablet. Stearic acid and magnesium and calcium stearates are considered insoluble. Magnesium stearate is one of the commonly used lubricants. It is white, very fine powder that is used in between 0.25-5% concentration. It is usually added at the last step of formulation processing, so that it will not be mixed for a long time with other formulation excipients to prevent hydrophobicity problems (Li & Wu, 2014).

As the best lubricants are hydrophobic, an increase in the time of disintegration and a decrease in the rate of drug dissolution can be caused by the presence of the lubricant coating. Usually, these undesirable effects increase as the concentration of the lubricant increases and as the capacity of water to enter the tablet is decreased. The presence of a lubricant can also interfere with particle-to-particle binding because the strength of a tablet depends on the area of contact between the particles, resulting in a less cohesive and mechanically weaker tablet. (Banker et al., 1980).

b) Water-soluble lubricants

Alternative more hydrophilic materials have been investigated due to the natural association of lubricant properties with lipophilic materials (and hence with poor aqueous solubility). Water-soluble lubricants are in general used only when a tablet must be completely water- soluble (e.g. effervescent tablets) or when unique disintegration or, more commonly, dissolution characteristics are desired. Sodium stearyl fumurate is considered to be a water-soluble lubricant.

Perhaps not surprisingly, none appears to possess as much lubricity as that of the water- insoluble lubricants, although synergism may be of help in some combinations.

2.4 Preformulation Studies

Preformulation testing is considered to be the first step in the development of dosage forms before the formulation. The main aim behind this study is to generate information regarding the drugs physical and chemical properties alone or in combination with excipients, to produce a stable and bioavailable dosage form (Verma & Mishra, 2016). In this section, there are a variety of important features that should be tested. They are usually the bulk properties of the powder, which includes for example, the densities of the powder, powder flow properties, melting point, hygroscopisity and solid state characteristics such as, particle size and surface area analysis. Moreover, solubility, powder consolidation properties and stability analysis are also performed (Kesharwani, 2017).

2.4.1 Incompatibility studies

Active drug/excipient compatibility studies represent an important step in the production of all dosage forms in the pre-formulation stage. Potential physical and chemical interactions between drugs and excipients can affect the chemical nature of the drugs, their stability and bioavailability, and thus their therapeutic effectiveness and safety. (Bharate et al., 2016; Rowe et al. 2009)

There are several techniques that study the morphology of the drug substance

and can determine the nature of physical transformations, thus indicating the type of incompatibility that has occurred (Sims et al. 2003).

Certain classes of compounds are known to be incompatible with particular excipients (Monkhouse & Maderich, 1989). Hence, knowledge of the chemistry of the drug substance and excipients can often minimize formulation surprises. (Bharate et al. 2016; Crowley, 1999)

Drug-excipient interactions/incompatibilities are major concerns in formulation development. Therefore, selection of the proper excipient during preformulation studies is of prime importance.

2.4.2 Particle Size Characteristics

Furthermore, the powder's solid state characteristics are crucial to understand since many processes such as bulk flow, formulation homogeneity, surface area and dissolution rely on the powder's characteristics. For example, the size, shape, size variability and hardness will all contribute to the flow properties. Therefore, it is very important to highlight the importance of particle size distribution and surface area of the powders as they resemble the solid state characteristics of the powder where they have an impact on the biopharmaceutical behavior. (size, shape, etc.) (Honmane, 2017).

For instance, if the particle size distribution of the active components and excipients suffer from un-uniform size distribution and de- mixing effects, this will impede mixing or if attained it will be difficult to maintain the mixing of the mixture during the following processing steps. There are several techniques obtainable that determine the particle size analysis, these include sieving, electron microscopy, laser diffractometry and light microscopy combined with image analysis (Etzler & Sanderson, 1995).

Likewise, surface area detection of the particles is also important to determine since they can have an impact on the dissolution rate as described by Noyes-Whitney equation. Surface area is usually determined when it is difficult to predict the particle size. They are usually determined by gas adsorption technique through Brunauer-Emmett-Teller (BET) analysis. The main idea behind this concept is the adsorption of

gases onto solid surfaces by forming physical forces or chemical forces of interaction (Dollimore et al., 1976).

2.4.1.1 Light Microscopic Analysis

Light Microscope is an equipment that scan the small particles which is not seen by unaided eye using lenses that magnify objects with the aid of visible light, and for the sake of importance of studying particle sizes and shapes before being used in industry light microscope is used (Bradbury et al., 1998).

2.4.1.2 Laser Particle Size Analyzer (Laser Diffraction)

"Laser diffraction measures particle size distributions by measuring the angular variation in intensity of light scattered as a laser beam passes through a dispersed particulate sample". "The parameter D90 should more correctly be labeled as Dv (90) and signifies the point in the size distribution, up to and including which, 90% of the total volume of material in the sample is 'contained'. "The definition for D50 or Dv(50), then, is then the size point below which 50% of the material is contained, and the D10 or Dv(10) is that size below which 10% of the material is contained. This description has long been used in size distribution measurements by laser diffraction." (Malvern Panalytical)

2.4.2 Powder Densities

Usually what determine the density of the powder are the handling conditions. There are three types of densities measured. Firstly, the bulk density is the density when the powders volume is at its maximum and has aeration between the particles. Secondly, tapped density is the density of the powder after the voids between the particles are removed by tapping. Finally, true particle density, is the density of the particles itself (the actual density of the solid material), it is mainly measured by the helium pycnometry (Honmane, 2017).

2.4.3 Flow properties of powders

Powder flow is described as the powder's ability to flow into a particular piece of equipment in the desired manner. The basic property of powders used for tableting is flowability (Prescott and Barnum 2000). In producing tablets with consistent weight and strength, good flow properties are significant. Flow properties of powders are primarily influenced by the surface, size and shape of particles as well as the distribution of particle size (Carr 1965; Staniforth 2002). External conditions such as air content and relative humidity (RH) have a direct influence on powder flowability (Hiestand 1984). During preformulation tests, powder flowability studies and flow property optimization should be carried out to minimize the impact of flow variations on the production scale (Lewis and Simpkin 1994).

It is a crucial characteristic in the pharmaceutical manufacturing, mainly because there are several manufacturing steps that require filling of the powders in containers, all of these steps involve several powder handling steps. For instance, blending, transfer of the powder, storage and feeding into the press all require the powder to have good flowing properties because lacking such property will result in dosage forms having poor mixing, content uniformity and uniform weight distribution. As a result, the inability to achieve reliable powder flow during these manufacturing steps will have a significant adverse effect on the manufacture and release of the product to the market (Patel, 2019).

There are a variety of factors that can impact the powder's flowability, in fact they could be classified into two groups, powder variables (i.e. particle size and distribution, shape, surface texture) or external factors (i.e. flow rate, compaction condition, humidity and storage time). Poorly flowablity can be solved either by selecting appropriate excipients or through pre-compression or granulation techniques (Chaurasia, 2016).

There have been many methods developed for the study of flowability. Measurements of packing and avalanching behavior or powder flow rate through orifice or funnel are the most common techniques (Kaye et al. 1995; Ph. Eur. 2002a). There is still not a single method that can explain the complexity of the powder flow.

Different techniques may be used in parallel to obtain a deeper understanding of powder flow properties (Lindberg et al. 2004; York 1983).

2.4.3.1 Angle of repose

It is defined as the maximum internal angle that exists between the surface of the powder pile and the horizontal surface. Tan θ = (h/r), where h resembles the height of the pile and r resembles the pile's base radius. The angle is in the range from (0-90). If the angle is found to be ≤30°, it is free-flowing whereas ≥40° indicates a poor flowing powder. It is mainly established using the fixed funnel method (Geldart et al., 2006). The ranges for this property are illustrated in (Table 2.2).

Table 2.2 Ranges for Angle of Repose (USP 31)

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

2.4.3.2 Carr's Compressibility index and Hausner's ratio

This parameter predicts the flowability of powders and their compressibility as described in (Table 2.4). It was proposed that the bulk density, surface area, size and shape, cohesiveness of the material and the moisture content of the powder, influenced as an indirect measure for the compressibility index. They are determined by measuring the powder's bulk and tapped volume through the following Equations (2.1 and 2.2) (Shah et al., 2008).

The United States Pharmacopeia (USP) and National Formulary (NF) define the compressibility index as "an indirect measure of bulk density, size and shape,

surface area, moisture content, and cohesiveness of materials because all of these can influence the observed compressibility index. They are determined by measuring both the bulk volume and the tapped volume of a powder" (USP 31).

The following equations are used to calculate the compressibility index:

$$\text{Compressibility index} = \frac{(\text{Tapped density} - \text{Bulk density})}{\text{Tapped density}} X\ 100 \qquad \text{(Eq. 2.1)}$$

$$\text{Hausner's ratio} = \frac{\text{Tapped density}}{\text{Bulk density}} \qquad \text{(Eq. 2.2)}$$

The table 2.3 below describes the ranges and characteristics of Carr's index and Hausener's ratio.

Table 2.3 Scale of Flowability (USP 31)

Compressibility index	Flow character	Hausner's 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 poor	>1.60

2.4.4 Solubility

Finally, solubility studies are known to be the first physicochemical property that has to be determined and this early determination eases the formulation of the drug candidate since it allows the formulators to understand the drug's properties. When

designing an oral dosage form it is preferable that the solubility should be above 10 mg/ml. On the other hand, if the solubility is noted to be less 1 mg/ml, and then it is declared as a problem (Honmane, 2017). Solubility of Ibuprofen is 21 mg/L (at 25 °C) (Yalkowsky & Dannenfelser, 1990).

2.4.4.1 Biopharmaceutical Classification System (BCS)

In order to develop an efficient and useful pharmaceutical product, it would be of great help to have a better understanding of the physicochemical and biopharmaceutical features of the drugs in choice. The Biopharmaceutical Classification System (BCS) is known to be a powerful tool in formulation development decision-making from a biopharmaceutical perspective (Amidon et al., 1995).

BCS is considered to be a scientific framework that categorizes the drug substances mainly based upon their aqueous solubility along with their intestinal permeability. By combining the drug product dissolution, the BCS takes into consideration three main factors that are responsible for both the rate and extent of drug absorption from an Immediate Release (IR) solid dosage form. These factors are known to be intestinal permeability, solubility, and dissolution. In BCS terms, drug substances are classified according to the following criteria (Reddy & Karunakar, 2011).

Class 1: High Solubility - High Permeability Drugs

Class 2: Low Solubility - High Permeability Drugs

Class 3: High Solubility - Low Permeability Drugs

Class 4: Low Solubility - Low Permeability Drugs

To begin with, a drug substance is classified to be highly permeable, when the absorption of the drug occurs with an extent of 90% or more of the administered dose. This extent of absorption was determined in the early stage of development by in vitro permeability assays using Caco-2, MDCK cells or artificial membranes, in order to

predict the drug's permeability initiating from the gut lumen ending into the bloodstream (Kawabata et al., 2011).

On the other hand, a drug is classified as highly soluble, when the highest dose strength determined for the drug is soluble in 250 ml or less of aqueous media over a pH range of 1-7.5 at a temperature of 37^{o}c.

Therefore, in the early drug development, the highest human dose estimated could be used alternatively in order to classify the solubility of the drugs. In addition, a drug substance is considered to be rapidly dissolving when 85% or more of the drug substance labeled amount dissolves in 30 minutes using (Reddy & Karunakar, 2011).

- The USP apparatus 1(basket) at 100 rpm or USP apparatus 2 (paddle) at 50 rpm.

- The dissolution medium volume of 900 ml or less in each of the following:

1. 0.1 N HCI or simulated gastric fluid (SGF) USP without enzymes.

2. A pH 4.5 buffer.

3. A pH 6.8 buffer or simulated intestinal fluid (SIF) USP without enzymes.

2.5 Powder Compaction and Particle Bonding

To withstand handling and storage, the optimum excipient should be able to form a successful compact with the intended drug. Friability, which should not be greater than 1 percent, is typically the strong indirect measure used to evaluate this property (see compact friability).

The process of compaction is a composite of several events: displacement of particles into empty spaces, fracture of particles, elastic deformation, deformation of plastics and cohesion between the surfaces of particles. These processes occur concurrently, but not necessarily to the same degree at any point of the compression process (Shlantha and Milosovich, 1964).

2.5.1 Particle bonding forces

A decrease in porosity occurs during the consolidation of a powder bed. This drop in compact volume places particles in close proximity to one another. The reduced distance between the particles allows bonds to be formed and allows the particles to adhere together into a cohesive compact. In direct compression of pharmaceutical materials, two distinct forms of interactions are usually considered: intermolecular interactions and mechanical interlocking. The most powerful intermolecular forces responsible for keeping the particles together in a tablet are probably the Van der Waals forces. Another instance of forces that work over a short distance between particles is hydrogen bonding. The essence of these forces depends on the material's chemical composition. Bonding depends on the surface texture and form of the particles by hooking or twisting of particles. The dominant bond form depends on various factors, including the degree of compression and the inherent properties of the material. In the high porosity range, the principal attraction between particles has been suggested to be intermolecular forces; while in the low porosity range, strong bridges play a major role (Adolfsson and Nystrom, 1996). By spanning, sintering, melting and crystallization, solid bridges typically link particles (Hiestand, 1997).

2.5.2 Powder compaction

Pharmaceutical powder compaction is a dynamic process requiring a detailed understanding of the fundamental properties of excipients, drugs and mixtures (Rippie and Danielson 1981). The powder particles are loosely packaged after the die of the tableting machine has been filled and before pressure is applied, and the powder density is similar to its poured density (York 1978). As the machine's punches travel closer to each other, the strain increases and the decrease in volume starts. Firstly, particles are rearranged so that the smaller particle is more tightly packed in the voids between the larger particles and the powder. Regularly formed particles are more readily rearranged than irregularly formed particles (York 1978).

Generally, powders when subjected to low compressive forces, the particles

will undergo rearrangement until they reach the point of tapped density, where no further reduction in the volume bed can occur without particles deformation. At such point, if the powder was subjected to further stress then the particles will start to deform elastically, whereas the force applied increases, the density increases as well. Any further reduction in the bed volume after exceeding the elastic limit will be mainly due to plastic or brittle fracture of the particles. The volume reduction occurs by reversible or permanent deformation or fragmentation of particles to smaller units when the initial rearrangement of the particles is completed and the pressure is further increased. The particle surfaces are brought closer to each other during the compression and interparticular attraction or bonding is formed. Brittle materials intend to have fragmentation where the voids are filled by the resulting fine particles that form a secondary packing and plastic materials tend to fill the voids by distorting themselves. Those two processes aid the bonding in order to form a single compact, where plastic flow tends to increase the contact areas irreversibly between the particles, whereas brittle materials turns out to produce clean surfaces that provide strong bonding. (Duberg and Nyström 1986)

The compacts usually undergo some degree of elastic recovery after the pressure is removed and the decompression stage starts (Nyström et al 1993).

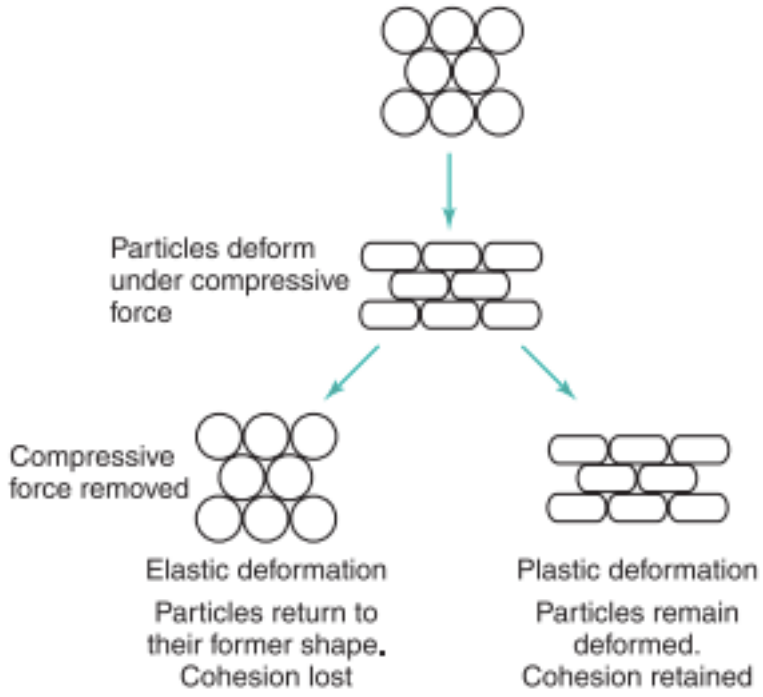


Figure 2.5 Illustration of Particle deformation during compression. (Aulton & Taylor, 2018)

The potential of the powder to undergo volume reduction under pressure is compressibility. The method of volume reduction and the degree of volume reduction of powders depend on the characteristics of both the mechanical properties and the volume reduction mechanism of the material concerned (Jones 1977). During the compression cycle, the volume reduction of powder takes place in several phases and the process of volume reduction differs during different phases (Duberg and Nyström 1986).

Compactibility is commonly seen as the capacity of powder to form a compact with sufficient strength (Fell and Newton 1970). Compactibility may also be attributed to the mechanical strength of compacts, so that the compression pressure used is related to the force used to diametrically split the resulting compact (Fell and Newton 1970). As the term compression is used to define the process of volume reduction, the term compaction encompasses the entire tablet forming process, including the formation of bonds (Duberg and Nyström 1986).

Investigating the powder consolidation properties under pressure (compaction properties) and understanding the protocol in which the bonds are formed between the particles are of great importance when designing formulations

2.5.3 Porosity Plots

Measurement of the volume reduction and the porosity of the powder as a function of the compression pressure is a method widely used to describe compaction process (Walker 1923). The porosity of the compact can be measured when the dimensions and weight of powder column are known and compared to the true density of the powder. The porosity can be derived from Equation 2.3.

$$\varepsilon = \frac{1-\rho_A}{\rho_T} \qquad \text{(Eq. 2.3)}$$

where ε is the porosity and ρ_A is the apparent density of the powder column and ρ_T is the true density of the powder.

The measurements of the porosity and the pressure are usually done with instrumented tableting presses or with a compaction simulator, where the displacements of the punches can be measured simultaneously with the compressive forces (Celik and Marshall 1989).

2.5.4 Force-Displacement (F-D) curves

Displacements and forces of punches of the tableting machine, can be used to determine the deformation behaviour and other mechanical properties of materials. This is one of the reasons why researchers attempted to measure the energy involved during the compaction of tablets (De Blaey & Polderman, 1971; Ragnarsson & Sjögren, 1985). Energy transferred by the upper and lower punches is utilised for particle rearrangement, elastic-plastic deformation and/or brittle fracture and breaking of bonds in the material. The proportion of the total energy applied to the material which has been absorbed by it, can be estimated from the area under an appropriate force-displacement curve (Celik & Marshall, 1989).

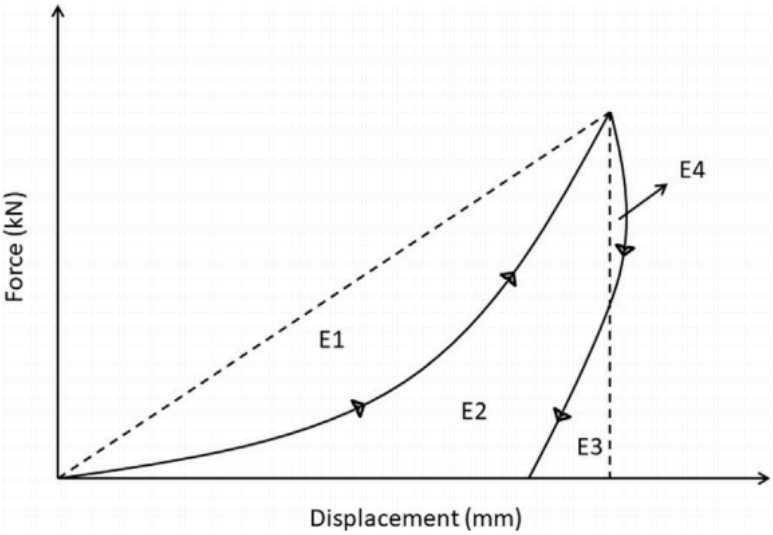


Figure 2.6 Force displacement curve, indicating the energy distribution during tablet compression. E1: rearrangement energy, E2+E4: plastic energy, E3: elastic energy, E4: plastic flow energy.

When the force-displacement curve of the compression cycle was studied, the different energetic parameters could be subdivided and calculated from the curve (Figure 2.6). As the upper punch first moves down into the die filled with powder, particle rearrangement takes place by having the particles slide over one another, reducing interparticulate distances without causing excessive deformation. (Martin et al. 2003; Nordström et al. 2009) The energy consumed to overcome this interparticulate frictional force was recorded as the rearrangement energy, presented by E1. As the applied stress increases to a stage where there is no more room for rearrangement, deformation occurs, which was recorded as plastic energy and presented as the sum of E2 and E4. As the upper punch ascends, the resultant tablet undergoes elastic recovery, and the release in elastic energy is presented as E3. Plastic flow energy represents the energy required for particle rearrangement after peak force has been achieved, presented as E4. (David & Augsburger, 1977). Compression energy refers to the energy provided by the tablet press to the powder for the formation of the compact and is the sum of E2 and E3, whereas total energy refers to the sum of E1, E2, E3, and E4 (Tay et al. 2019).

2.5.5 Powder Consolidation Models

Studying the relationship between compact porosity and compression pressure will assess the evaluation of powder compressibility. Awareness of a powder's volume reduction potential allows the compaction behavior of a pharmaceutical substance to be predicted (Bassam et al., 1990).

To explain the aggregation or volume decrease of powders, mathematical models were used. These models were developed from empirical mathematical relationships and were based on the suggestion that different processes occur in different application pressure ranges (Kennedy et al., 1996). Such models are used for compact production to classify tablet excipients. The predominant behavior of powder densification and deformation (plastic, brittle and elastic) is also identified and explained (Picker, 2000).

2.5.5.1 Heckel analysis

The Heckel equation is the most commonly used tool for the study of pharmaceutical substance deformation behaviors (Roberts and Rowe 1986). By analyzing plastically deforming metal powders, Heckel (1961) developed the equation. He suggested that the reduction in metal powder volume is similar to first-order chemical reaction kinetics. From his equation (Eq. 2.4) for a variety of metal powders, Heckel also found an empirical relation between the yield strengths and the constant K. Identification of the phases of consolidation, deformation and compaction is possible from the relationship between compression pressure and powder column density. In fact, this form of equation was first suggested by Shapiro (1944), who also suggested that a first-order type of reaction with applied pressure obeys the reduction in porosity.

As a function of compression pressure, the change in the density of the powder column is inversely related to the change in the porosity of the powder column, according to the Heckel equation (Eq. 2.3). (Heckel 1961a). The following form is taken from the Heckel equation:

$$\ln \frac{1}{1-D} = \mathrm{K} \times P_{compression} + A$$

(Eq. 2.4)

The relative density of the powder column is divided by the true density of the powder at compression pressure P in Heckel equation D. Constants A and K are determined from the extrapolated linear component of the ln(1/1-D) plot versus P compression, the intercept being A and the slope being K (Fig. 2.2).

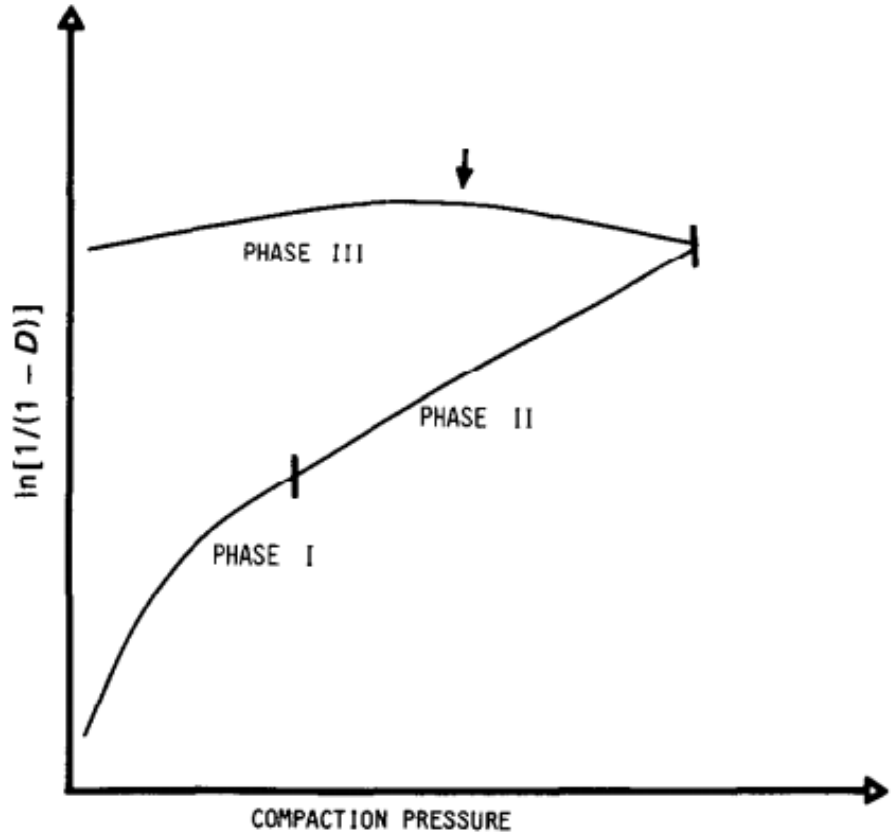


Figure 2.7 A typical example of a Heckel profile during compression and decompression of a powder (Duberg and Nyström 1986).

The Heckel profile can be split into three stages: (Fig. 2.7). The volume reduction in stage I is caused by the rearrangement of particles as the smaller particles fill the voids between the larger particles (Heckel 1961a). The breakup of the primary particles at lower pressures or the presence of agglomerates of the primary particles is

another explanation of the nonlinearity of this point (Denny 2002). The compression step is Phase II, where volume reduction is the result of plastic flow or fragmentation of the material deformation. When the compression pressure is relieved, step III is indicative of the elastic expansion of the material (Duberg and Nyström, 1986; Paronen 1986).

The constant K value provides details about the plasticity of the powder (Heckel 1961a). As the value of slope K increases, plasticity increases. Mean yield pressure (Py) is a value representing the resistance of materials to deformation (Hersey and Rees 1971). Equation 2.5 relates the mean yield pressure to the constant K(Hersey and Rees 1970):

$$P_y = \frac{1}{K}$$

(Eq. 2.5)

For plastically deforming materials that have lower deformation resistance, the yield pressure values are typically lower. Py-values of 47.6 to 104 MPa were obtained for microcrystalline cellulose (Paronen 1986; Roberts and Rowe 1987). Yield pressure values are higher for brittle materials. For example, the Py values calculated for -lactose monohydrate usually range from 150 to 200 MPa (Ilic et al. 2009).

It is necessary to define precisely the linear part of the Heckel plot for the determination of the value of K. The linear component is generally defined by taking the plot's first and second derivatives (Roberts and Rowe 1985). The first derivative for the linear component is constant, and the second derivative is zero. In some materials, the curvature nature of the Heckel plot prevents the determination of the linear portion of the plot (Roberts and Rowe 1985).

Data from the Heckel study can be obtained using two methods, the tablet-in-die method (at pressure) and the ejected tablet method (at zero pressure) (Fell and Newton 1971; Heckel 1961a). The applied pressure and the packing fraction of the powder column are determined at several points during one compression cycle in the tablet-in-die-method The maximum upper punch pressures and packing fractions are often used in the ejected tablet technique, but the packing fraction is determined by calculating the tablet measurements after ejection from the die (Fell and Newton 1971; Heckel 1961a).

As used for pharmaceutical products, Heckel analysis has several restrictions. Heckel did his metal studies, and organic solids' deformation behavior is somewhat different from that of metals (Duberg and Nyström 1986). Only a small part of the overall densification occupies the area where the Heckel plots are linear, and it is difficult to describe the linear part of the plot for certain materials. The parameters obtained from the Heckel equation are not valid and reproducible material constants, Sonnergaard (1999) says. It is also stated that, because of the elastic component, the yield pressure value does not inherently reflect the plastic deformation of materials and is in any event overestimated. The Heckel analysis depends on the experimental conditions and small errors can cause major variations in the Heckel parameters measured (Sonnergaard 1999). For example, the yield pressure values calculated by different authors differ considerably. For instance, the Py values measured for microcrystalline cellulose (Avicel PH 101) are between 47.6 MPa and 104 MPa (Paronen 1986; Roberts and Rowe 1987).

It is of high importance to correctly evaluate the true density values used in the Heckel analysis. One percent error in the true density values in the calculated yield pressure values will cause a 10 percent error (Gabaude 1999). Accurate punch displacement measurement and machine deformation corrections are critical. The maximum pressure of compression determines the yield pressure values (Paronen 1986; Rees and Tsardaka 1994). Ragnarsson et al. (1984) proposed that the mean upper and lower punch forces be used for the compression pressure values used to measure the Heckel profile.

Attempts were made to strengthen the methods for evaluating the plots of Heckel. For instance, Krumme et al. (2000) indicate that certain important issues should be taken into account when using the Heckel analysis. The height accuracy of the powder bed in all conditions should be higher than 10 μm (+-5 μm) in order to correctly calculate the relative density. It should also be better than +-5 μm for deciding the die diameter. The true content density should be measured using very high-pressure tests and the measurement accuracy should be higher than +- 0.01 g/ml. It is recommended to correct machine deformation by compression of solids, but it is less important.

Using the Heckel analysis, the determination of the deformation behavior of

materials can be achieved simply by measuring yield pressure values, but some other methods have also been suggested. It was shown that particle size had an effect on the determination of Heckel profiles (Hersey and Rees 1970; Roberts and Rowe 1986). As various fractions of particle size are compressed, different behaviors in Heckel plots are shown to fragment and deform materials plastically (Figure 2.8). For different size fractions of the same material, Heckel plots for plastic materials remain parallel for the entire compression pressure spectrum (Type 1). The Heckel plots display coincident linear relationships for fragmenting materials (Type 2) when the initial structure of the powder bed is broken (Hersey and Rees 1971).

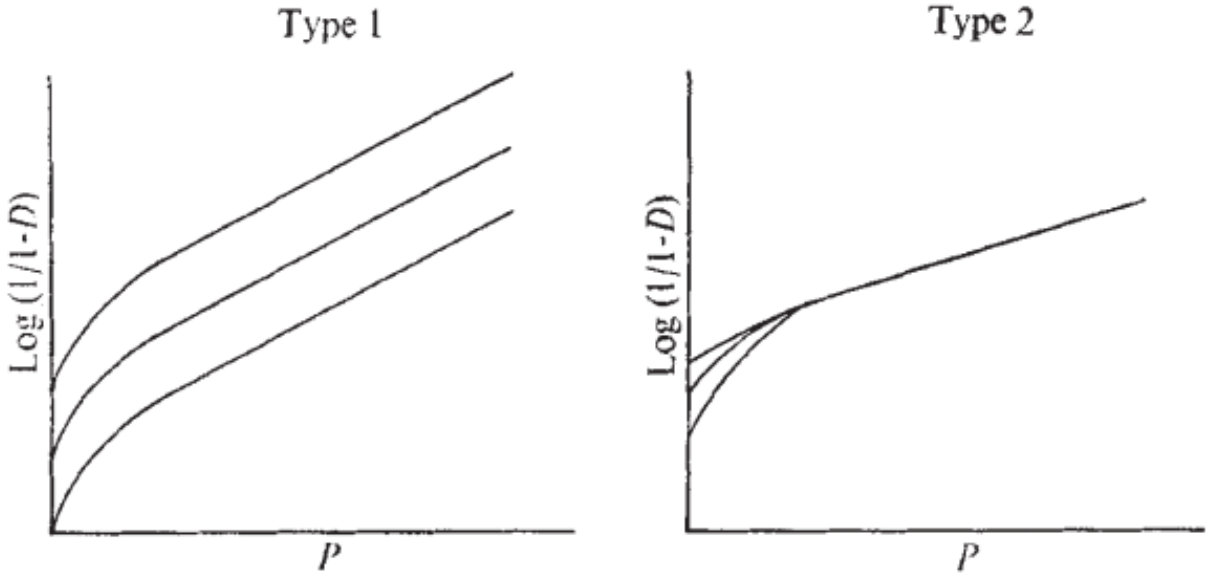


Figure 2.8 Heckel plots for different size fractions of plastic (Type 1) and fragmenting materials (Type 2) (Hersey and Rees 1971)

2.6 Mechanical properties of powders

The effectiveness of powder compaction is determined by the mechanical properties of materials and the deformation behavior of the material is a property that mainly affects powder tableting. Three mechanisms of volume reduction, plastic deformation, brittle fracture and elastic deformation, are widely accepted. For any material used in tableting, the deformation mechanism and behavior during compression are unique (Roberts and Rowe 1986).

Plastic deformation is a permanent kind of material deformation. Plastic deformation at the particle level can be described as a change in the shape of the particles. Plastic deformation involves breaking a finite number of atomic bonds in particles of crystalline solid material by movement or dislocation of parallel crystal planes (Saada 1999). Plastic deformation is controlled by applied stress. The stress is the force applied on a compact or powder divided by the surface area of a compact. The stress applied to the powder bed causes a change in dimensions of the compact. Magnitude of this dimensional change is called strain. Materials considered plastic are for example sodium chloride, microcrystalline cellulose and many starches (Hardman and Lilley 1970; Roberts and Rowe 1986). Many researchers have shown that ductile materials that deform mainly plastically have a compression rate dependency that affect the tensile strength of tablets. The compression rate dependency is caused by the fact that plastic materials are able to undergo some degree of stress relaxation during the compression cycle (Roberts and Rowe 1985).

Elastic deformation is time independent and reversible. All materials undergo some degree of elastic deformation under pressure (Marshall 1986). Elasticity of materials used in tableting is important factor to take into considerations. A high degree of elasticity is not a desirable quality for materials because the elastic expansion of compact after pressure is removed can lead to weaker tablets due to breakage of bonds between particles (Roberts and Rowe 1996).

Fragmentation of particles means dividing of the crystalline particles to smaller secondary particles under pressure (Duberg and Nyström 1982). In particle level, fragmentation begins at the point called Griffith crack, where particle has surface flaws (Griffith 1921). Fragmentation occurs as applied pressure rises, when stresses inside the particle grow until the critical stress of the weakest flaw is reached (Mott 1945). The cracking of the particles is depending on the particle shape and size as well as the crystal structure (Duberg and Nyströn 1982). Typical examples of the brittle fragmenting materials are crystalline lactose and sucrose (Roberts and Rowe 1985). The fragmenting materials have some advantages in tableting over plastic materials. It has been shown that the fragmenting materials are less sensitive to the initial particle size, shape and texture (Alderborn and Nyström 1982a). Fragmenting materials are also insensitive to the compaction rate and they cause fewer problems in scaling up

the manufacturing (Roberts and Rowe 1986). Fragmenting materials are also less sensitive to amount of lubricants used as well as the lubricant mixing time than the plastic materials. Fragmentation of particles creates new clean surfaces for bonding that are not covered with a hydrophobic layer of the lubricant (De Boer et al. 1978). Materials are usually classified as brittle or ductile depending on their main deformation behaviour, although all materials undergo some degree of plastic, elastic and fragmentation during compression cycle (Duberg and Nyström 1986). The main deformation mechanism also depends on material properties, such as particle size, and process parameters such as compression speed and compression pressures (Roberts and Rowe 1985).

Generally, the plastic deformation is considered to be a desirable property for materials used in tableting as the plastic flow creates wide contact areas between particles (Benbow 1983). Materials deforming through plastic flow form stronger tablets with lower compression pressures than brittle materials. This is because dislocation and movement of parallel crystal planes consume less energy than breaking all atomic bonds at once during fragmentation (Tye et al. 2004).

Some degree of fragmentation of particles is also important because it creates new contact points for particles (Leuenberger et al., 1989). In tablet formulations brittle excipients are usually needed when the drug is ductile and ductile excipient when the drug is brittle (Wells and Aulton 1988).

2.7 Compaction Simulator

Compaction simulators are defined as a device capable of mimicking in real-time, the exact cycle of any tablet press and recording the parameters. It enables a new approach in tableting research and is used to study powder compaction behaviour and fundamental material characterization using different compression parameters such as compression force and punch displacement (Reugger & Celik 2016). Simulators have the ability to reproduce upper and lower punches displacement profiles in order to get information about powder compressibility.

They are multifunctional equipments that can assist in all phases of the pharm aceutical industry's drug development and production (Celik, 2016; Celik and

Marshall, 2010; Michaut et al., 2010).

There are several types of equipments that provide the powders compaction in the pharmaceutical area and they mainly include single-press, rotary-press and the compaction simulator. Ibuprofen formulations were directly compressed using the compaction simulator (Stylcam 200R).

It is also known as computerized hydraulic press. It is composed of a single punch system in which both the upper and lower punches are individually driven through hydraulic rams which are controlled by a computer. The machine has the ability to mimic the exact cycle involving any tableting process in real time and to be able to record all the critical parameters during the cycle (Çelik and Marshall., 1989).

Compaction simulator is a machine developed for mimicking cycles and function of any tablet press and records parameters, for example: force, displacement which are crucial for evaluation of compaction procedures. It's single station tablet press where the punches comply with programmed cam made to simulate rotary tablet press (Çelik and Marshall, 1989).

In the compaction simulator the tablets are prepared under restricted conditions. For instance, the punches can be considerably controlled and varied. There are various applications that can be served through such machine. For example, the sensitivity of the drug to such variations (such as force) can be investigated. In addition to, the loading pattern of production presses can be mimicked in order to predict any future scale-up obstacles that may be present by using only small quantities of the materials needed (Jain, 1999).

Table 2.4: Comparison of equipment for tableting studies (Çelik and Marshall, 1989).

Feature	Single station press	Multi station press	Punch and die set	Simulator
mimic production conditions	no	yes	maybe	yes
mimic cycles of many presses	no	no	maybe	yes
require small amount of material	yes	no	yes	yes
easy to instrument	yes	no	yes	yes
equipment inexpensive	yes	no	maybe	no
easy to set up	yes	no	maybe	maybe
data base in literature	yes	yes	some	no
used for stress / strain studies	no	no	yes	yes

2.8 Formulation Evaluations

2.8.1 Quality Control Tests

Tablet quality control tests are performed to guarantee the production of a perfect tablet (Gibson, 2016). The following properties are studied during and after tablet manufacturing to be certain it meets the standards and that all batches are bioequivalent (USP35).

Certainly the quality of the final product is not just a random incident; it is the result of well controlled procedures. As a result, an important step is to assess the tablets quality with respect to the specifications stated in the pharmacopoeias and accordingly the quality parameters will be assisted if they are within the acceptance limits or not.

Out of these tests, certain tests are mentioned and described in the pharmacopoeias these are known as compendial tests including weight variation, dissolution, disintegration and the content uniformity (USP35).

On the other hand, the tests that were not mentioned in the pharmacopoeias are known as non-compendial tests, such as the hardness and friability of the tablets (Allen & Ansel, 2013; USP35).

2.8.1.1 Uniformity of Dosage Units

The purpose of this test is to ensure that the consistency between the dosage units is achieved, this is vital because each unit should have the active drug within a limited range around the label claim. This can be achieved through measuring the content uniformity or through weight variation test (Zaid et al., 2013).

The weight variation test can be applicable for uncoated tablets, film coated tablets and hard capsules that contain 25 mg or more of the drug substance of the dosage unit. All International Conference on Harmonization (ICH) regions considered the weight variation test as an alternative for the content uniformity test given that the

25 mg threshold is met (Zaid et al., 2013).

2.8.1.1.1 Weight Variation

A method to guarantee that each tablet includes the right quantity of medication. Tablet weight depends on the volume of the material that occupy the die in the pressing machine. After determining the excipients measurements, tablet weight is set. Throughout the manufacturing process, random tablets are taken out for appearance evaluation and weighing (USP35).

Table 2.5 Weight variation tolerance for uncoated tablets

USP standards	Maximum percentage of allowed difference
≤ 130 mg	10%
130 mg – 324 mg	7.5%
≤ 325 mg	5%

If 20 tablets were weighed, only 2 tablets or less could be not in the percentage range and not over 2 times the percentage limit.

2.8.1.2 Disintegration

When a tablet breaks into little pieces due to the entering of an aqueous liquid into the small pores of the tablet, this phenomenon is described as Disintegration. Tablet disintegration test is done to check if the dosage unit disintegrates in the range of time documented after being put in a fluid medium while maintaining the standard conditions (Allen & Ansel, 2013).

In order to achieve the optimum bioavailability, first the drug should be available for absorption and for this to occur the tablets must primarily disintegrate

and liberate the drug to the body fluids for dissolution to take place. Although, this test does not usually guaranty a correlation with in vivo behavior, drug uptake and acceptable clinical effect, but if the tablet fails to comply with this test, then it is unlikely to be an efficacious dosage form (Taylor & Aulton, 2013).

Disintegration depends on numerous production aspects, such as the particle size of active ingredient in the formula, the type and temperature of medium used, the worker's knowledge, how soluble and hygroscopic the formulation is, type of diluent, amount of disintegrate and binder their categories and used technique of incorporation, the amount of lubricants and duration of their mixing, force of compression used, the production technique especially compacting of granules and pressing strength needed in making the tablet. It has been shown that there is an association between physical features with tablet disintegration time with tablet disintegration forces decreasing if aqueous fluid penetration forces decreased, which leads to requiring a longer time to disintegrate (Narazaki et al, 2004). Lubricant is known to have an effect on disintegration, the higher quantity of hydrophobic lubricant in a tablet, the more time it needs to disintegrate (Gupta et al., 2009). The higher the tableting pressure the longer the disintegration time will be as long as it is less than the crucial capping pressure (Harada et al., 2006.)

2.8.1.2.1 Disintegration Apparatus

According United State Pharmacopeia the apparatus contains a basket-rack assembly, a 1 liter, low-form beaker, 138 -160 mm in height and an inside diameter of 97-115 mm for the immersion liquid, a device to keep the medium's temperature between 35-39 Celsius, and a device for raising and lowering the basket in the immersion fluid at a constant frequency rate between 29 and 32 cycles per minute through a distance of not less than 53 mm and not more than 57 mm.

Regarding the amount of liquid medium, the top of the rising stroke the wire mesh should be kept under the surface of the liquid by ≥ 15 mm and the descending stroke should drop by ≥ 25 mm from the lowest point of vessel. The highest point of the basket-rack assembly must not be immerged at all throughout the process. The rising and falling strokes must be given the same amount of time and switching

between strokes should be done smoothly and not suddenly. The movement in this apparatus is vertically along the basket-rack assembly axis. The basket-rack assembly contains six see-through tubes with one side open, each of them is 77.5 ± 2.5 mm in length and an internal diameter of 20.7 - 23 mm and a wall thickness ranging from 1.0 to 2.8 mm in addition to 2 plates that are responsible of holding the tubes vertically with each plate's diameter ranging from 88 - 92 mm and is 5 to 8.5 mm thick, and it contains 6 punctures, each of them is 22 to 26 mm in diameter, in the middle of the plate and similarly close to each other.

There is a cloth made of stainless-steel wires waved together placed at the bottom of the lower plate, and a mere square weave that has holes and a wire that has a diameter of 0.57 to 0.66 mm. The pieces of the apparatus are collected and firmly held by 3 screws that go through the 2 plates. Disks should not be used unless it was acceptable in the monograph. If stated in the individual monograph, every tube comes with a cylindrical disk, its thickness is 9.5 ± 0.15 mm and its diameter is 20.7 ± 0.15 mm. It should be built of an appropriate plastic substance. There are 5 holes at the bottom of the cylinder. On the cylindrical axis there is one of the four holes, the remaining holes are made in the center 6 ± 0.2 mm away from the axis on made-up lines vertical to the axis and parallel to each other. Disk surfaces should not be coarse. Normally, the apparatus constitutes of six chambers, where it has cylindrical tubes having an open end at one side and the other side is closed by a 10-sized mesh screen (Hymavathi et al., 2015). According to the European pharmacopeia, disintegration is considered to be fulfilled, when the no more residues are left on the screen or if present, the residue should be a soft mass having no firm or unmoistened core or can be the remaining fragments of tablets coating (European Pharmacopoeia, 7th edn, 2011).

2.8.1.3 Dissolution

It is defined as a test done under special restrictions to assess the needed time for a certain amount of the medication to dissolve into solution (Anand et al., 2011). This test is performed in to vitro to come out with an accurate expectation of how bioavailable the tablet is in vivo are and to inspect how stable the tablets will be after a brief and extended time (Gad, 2008). Throughout the test, the drug will be released from the dosage form cumulatively into the solution and this will be measured as a function of time (Savale, 2017).

Dissolution can be affected by numerous factors, such as physicochemical features which include particle size, the total area of the tablet surface, how soluble the drug is, acid dissociation constant, molecular size, formation of salt, and surface tension (Murthy and Ghebre-Sellassie, 1993).

Physical factors also contribute in changing dissolution, they include viscosity and density. Formulation factors such as the choice and quantity of excipients, lubricant kind and mixing period, and type of dosage forms also affect dissolution (Gao et al., 2007).

According to the United States Pharmacopoeia there are two main kinds of apparatus for classic dosage form: Apparatus I (Basket), and Apparatus II (Paddle). (USP35)

2.8.1.3.1 Apparatus-I: Basket Apparatus

The apparatus assembly contains the following as seen in (Figure 2.9). In the rotating basket method, the tablet is put in a stainless steel basket that rotates at a fixed speed usually ranges from 50 to 100 rpm, this basket is dunked in cylindrical vessel with a convex end made of a transparent material such as glass which usually contains 0.9 L or 1 L of the medium that reached the desired temperature (37 ± 0.5 °C) in which the tablet will dissolve. Any increase or change of the media can result in an alternation in the pH or the composition.

This apparatus also contains a motor and a metallic drive shaft. To examine the ratio of the dissolved tablet, portions of the medium are taken for evaluation at scheduled times. It has many similarities with the paddle. The similarities are mainly the vessel characteristics and the water bath used. It differs mainly in that the stirrer contains a vertical shaft to which the lower part has a cylindrical basket attached. The basket consists of two parts: the upper part is attached to the shaft and has 3 spring clips to prevent the removal of the lower part of the basket and firmly holds it during the rotation. The lower part of the basket is formed into a cylinder of welded-seam cloth with a narrow sheet of metal around the top and bottom. The specimen to be tested is placed inside the basket. During the test, the basket's bottom will be 25 ± 2 mm from the inner bottom of the vessel and similarly as the paddle, the upper part of

the shaft will be connected to a motor with a speed regulator.

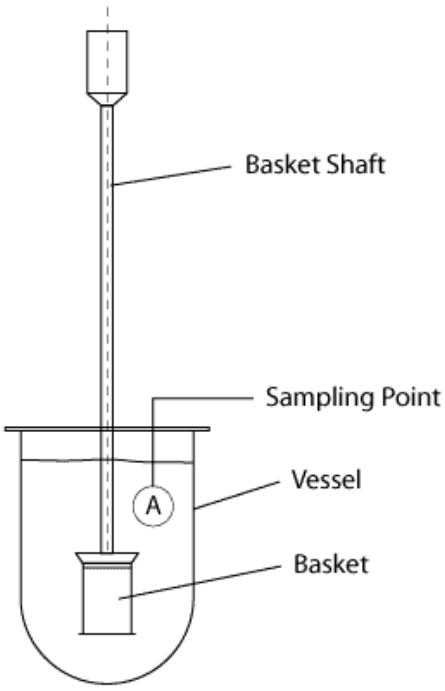


Figure 2.9 Basket Apparatus.

2.8.1.3.2 Apparatus-II: Paddle Apparatus

As seen in (Figure 2.10), the apparatus assembly contains a cylindrical vessel made of transparent glass that has a hemispherical bottomed shape and a maximum capacity of 1000 ml. There is a cover fitted above the vessel in order to retard evaporation. In paddle method, the tablet is put on the base of the vessel, and for mixing the components a paddle rotating at a specific speed, usually at the rate of 50 to 150 rpm is used (Bocanegra et al., 1990). To accommodate the shaft of the stirrer, the cover has a central hole and other holes where the thermometer and the instruments used to withdraw liquid can pass through. Moreover, it contains a stirrer that consists of a vertical shaft and to which the lower end of this shaft has a blade attached. The blade passes mainly through the diameter of the shaft in a way that the bottom of the blade is flush with the bottom of the shaft. The shaft's is positioned so that its axis is within 2 mm of the vessel's axis provided that the bottom of the blade is 25 ± 2 mm from the inner bottom of the vessel. Nevertheless, a motor is connected to the upper

part of the shaft with a speed regulator and the rotation of the stirrer is smooth with no significant wobble. Finally, there is a water bath that usually maintains the dissolution medium at 37 ± 0.5 °C. To examine the ratio of the dissolved tablet, portions of the medium are taken for evaluation.

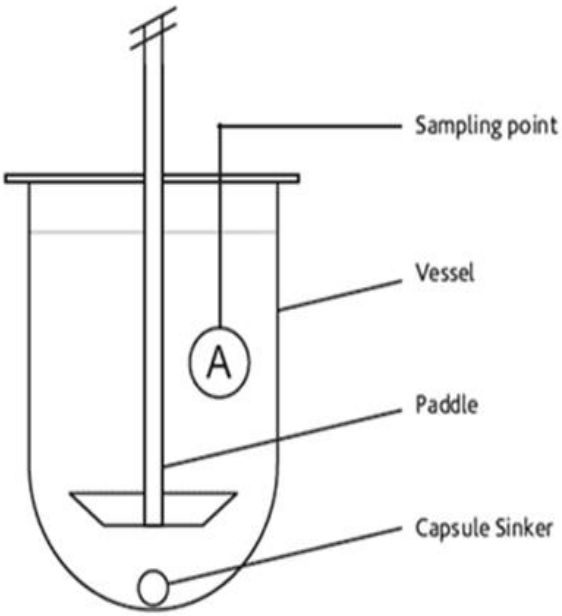


Figure 2.10 Paddle Apparatus.

2.8.1.3.3 Dissolution medium

Drug solubility determines the required amount and type of medium needed for dissolution. Solvent type is chosen according to the individual monograph. Buffered solutions can be used as a medium, in this case it is altered so that the pH is ± 0.05 of the given pH.

2.8.1.4 Friability of Uncoated Tablets

A method to inspect how resistant a tablet is to cracks and scratches after being compressed due to production process, transport, handling or storage conditions (Paul and Sun, 2017). One of the most critical properties of tablets, is that they should possess an ability to resist attrition forces faced through their shelf life period in order to be certain of the amount of drug being administered and that tablets shape do not change during their handling.

The main intention behind this test is to mimic the forces that may face the tablets during their production, handling and shipment, since during these processes the tablets may have collisions due to the tablets sliding over each other and lead to loss of some particles of their surfaces.

A tablet is considered friable when it erodes mechanically when handled (Uddin et al., 2015). The friability machine consists of a drum having specific diameter and depth with one side of the drum being removable. The weight percentage loss should not be more than one percent (European Pharmacopoeia, 7th edn, 2011).

2.8.1.5 Hardness

Another property related to the tablets to withstand the pressures from the surrounding factors during handling and production protocols is the hardness of the tablets. What really determines the hardness of the tablets is related to the amount of pressure that is faced by the tablet when pressed. Commonly, as the pressure applied increases, so does the hardness of the tablets produced. The tablets should be made sufficiently hard to withstand the handling and yet be soft enough to allow proper disintegration. The hardness tester under which defined conditions determine the resistance to the crushing of tablets. This is measured by the force required to crush the tablets in Newton (Allen & Ansel, 2013).

2.8.1.6 Thickness

This is a characteristic that is mainly determined by the die's diameter, the amount of fill allowed to enter the diameter, the compaction characteristics of the

material used to fill the die and finally the force and speed applied during the compression process. Producing tablets with uniform thickness is not just important for the appearance of the final product but also to make sure that every production lot can be packed by the same criteria. Thickness can be measured either through hand gauge or by an automated equipment (Uddin et al., 2015).

2.8.1.7 Tensile Strength

As tensile strength calculations depend on thickness and diameter of the tablet, and indicate the strength in directions, the tensile strength describes tablet strength more accurately than hardness (Jarosz and Parrott, 1982). It expressed by (MPa) unit. Because the crushing strength measurements do not take into account tablet diameters it is necessary to use the tensile strength measurement instead when the tablets with different sizes and shapes (Fell and Newton 1970). The radial tensile strength can be calculated from equation (Eq. 2.6):

$$\sigma = \frac{2F}{\pi.D.T}$$

(Eq. 2.6)

where σ is the tensile strength, F is the crushing strength, D is the diameter of the tablet, and T is the tablet thickness.

2.9 Quality by Design Approach

As commonly known, the product development stage is quite complex, requires intensive knowledge and in turn lots of time. Lately, the pharmaceutical industry witnessed major developments in production information, quality management systems and risk management, which in turn lead to the production of modern tools that aid in ensuring quality production. These tools usually aid the manufacturers in identifying, analyzing, correcting and preventing problems, which

will regularly improve the production processes (ICH Q8 guideline).

Recent advances in computer science and mathematics lead to the development of methods that helped in data analysis, as a result, a variety of software products that are based on mathematical models were developed to help streamline the developmental process. A number of these techniques used to optimize the pharmaceutical formulations include genetic algorithms, fuzzy logic and neural networks (Rowe & Roberts., 1998).

In this framework, a new concept of Quality by Design (QbD) was introduced into the pharmaceutical industry by the ICH (International Conference on Harmonization) guideline Q8 that was published in 2005.

Quality by Design (QbD) is characterized as a systematic and scientific risk-based approach to the production of pharmaceutical products and processes that targets consistent performance/quality of drug products and subsequently cost reduction as a major result (3,24). As commonly known, the product development stage is quite complex, requires intensive knowledge and is time-consuming. In this process, multivariate interactions are involved between raw materials and process conditions. For the processability and consistency of the finished product, these interactions are very critical (Aksu et al., 2013).

The modeling of Ibuprofen tablet formulation and production using modern science and risk-based techniques has many advantages over conventional modelling techniques, especially in the assessment of nonlinear relationships, which are frequently observed in pharmaceutical operations. QbD approach is used to enhance the understanding of how the critical quality attributes relate to the overall quality of the drug product by applying various formulation parameters to the filler and lubri cants (Aksu et al., 2013).

Following a QbD approach will result in an increased level of drug product consistency and minimize uncertainty. (Chudiwal et al., 2014). The most important aspect of QbD is to be aware of the effect of processes and formulation parameters on the characteristics of the product and to optimize these parameters according to the final required specifications (Lawrence, 2008).

Several QbD related studies have studied the influence of excipients on the performance of drug products, either by changes in the amount of excipients in the formulation or through the use of alternative excipients. The selection of appropriate functional excipients and their corresponding levels in the formulation of the drug product is critical to the performance of the drug product. (Kushner et al., 2014).

2.9.1 Development of QbD Approach

Mainly, pharmaceutical industries manufacture their products through the commonly known conventional approach that has been used for several decades. This approach is accomplished mainly by producing batches that can have their quality controls tested on the final product obtained at the end. Through this approach, several pharmaceuticals have been produced and served for public for several years.

However, using this approach nowadays has limited the evolving of the pharmaceutical product development due to the criteria that's implemented in this approach. Over here, the main idea is based on producing products that lie within a narrow scope of specifications as described by the U.S Food and Drug Administration (FDA) and mainly these specifications will be based on the batch history (Mesut et al., 2015).

As a result, the product produced will have its quality assured by inspecting and testing it at the end, but this does not guarantee that the product will always have the quality that it was designed for the first place since the whole idea is based on trial and error and not science based. Moreover, if any post approval changes are to occur during the manufacturing, then paper works should be filed in order to request for these changes, which in turn leads to time consumption and economical loss (Aksu and Mesut, 2015).

On the other hand, novel strategies have been implied to enhance the pharmaceutical development in a way that guaranties the production of a quality drug product that delivers the therapeutic benefit to the patient as claimed by its label. Therefore, a novel approach named Quality by Design (QbD) was proposed by the FDA and has been used recently in the pharmaceutical production.

2.9.2 Regulatory Aspects

2.9.2.1 International Conference on Harmonization Guidelines (ICH)

The International Conference on Harmonization Guidelines (ICH) is an initiative that unites regulatory authorization and pharmaceutical companies to regulate technical and scientific characteristic of drug development and registration. The ICH involved organizations and experts in Europe, USA, and Japan from the pharmaceutical manufacturers to set the practical specifications for licensing and registering the drugs and products among the three regions. Through the years, QbD has developed with establishment of ICH Q8 , ICH Q9, and ICH Q10, each will be explained alone in this index (Aksu and Yegen, 2014).

The aim of ICH is to provide public health through obtaining agreement by developing Guidelines and demands for pharmaceutical product documentation.

2.9.2.2 Pharmaceutical Development ICH Q8 (R2)

This section mainly talks about provides understanding by applying scientific base method and quality risk assessment to the development of drug and its manufacturing process. It presents the idea of Quality by Design (QbD) and how to develop this approach with design space (ICH Q8 Guidline).

2.9.2.3 Quality Risk Management ICH Q9

In this guideline, a systematic method for assessing and controlling quality risks is illustrated. It is applied through drug life period, developing, distribution and manufacturing. It is a scientific based assessment of risk that may develop through production (ICH Q9 Guideline) (Aksu et al., 2013).

2.9.2.4 Pharmaceutical Quality System ICH Q10

According to ICH Q10, the Pharmaceutical Quality System is "one comprehensive model for an effective pharmaceutical quality system that is based on International Standards Organisation (ISO) quality concepts, includes applicable Good Manufacturing Practice (GMP) regulations and complements ICH Q8 and ICH Q9". "ICH Q10 demonstrates industry and regulatory authorities' support of an effective pharmaceutical quality system to enhance the quality and availability of medicines around the world in the interest of public health" (ICH Q10 Guideline).

2.9.3 Elements of QbD

1- Quality Target Product Profile (QTPP): includes the quality characteristics of the products that intended to manufacture, forms and strengths of the dosages for example, with assuring safety and efficacy. So here we are thinking about the end product in the early stages of the beginning. In this way the critical quality attributes (CQAs) of the medication is well described.

2- Critical Quality Attribute (CQAs): A CQA has been defined as "a physical, chemical, biological, or microbiological property or characteristic that should be within an appropriate limit, range, or distributed to ensure the desired product quality"

The expected drug products CQAs obtained QTPP and previous well information applied to drive the process development with taking in consecration to adhere with suitable limits and bounds to guarantee the required quality.

3- Critical Material Attributes (CMAs): Includes all properties and characteristics of the drug as an input that intended to get, physical, chemical, ...etc. CMAs should adhere with suitable limits and bounds to guarantee the required quality either excipients or drug substance.

4- Critical Process Parameters (CPPs): Parameters that can influence the CQAs which observed prior or while process that affect manifestation, defect, and output of terminal product. In fact, the process parameters are different, some of them have higher influence on CQAs than the other, so it is important to identify CPPs with high impact over other process parameters. CPPs should be strictly controlled out of process parameters (Aksu and Mesut, 2015). Critical Process Parameter (CPPs) - } Critical process parameters (CPPs) are defined as "parameters whose variability have an impact on a CQA and therefore should be monitored or controlled to ensure the process produces the desired quality" } Process robustness is defined as the ability of a process to demonstrate acceptable quality and performance and tolerate variability in inputs at the same time.

2.9.4 Steps in QbD Approach

QbD approach consists of several steps:

- Quality Target Product Profile (QTPP), through which the critical quality parameters (CQA) of the product are identified
- Product design and understanding by identifying critical material attributes (CMA), i.e. the active substance (AS), the excipients, and the intermediate products
- Process design and understanding by identifying critical process parameters (CPPs) and a thorough process understanding aimed at successful and efficient process scale- up through linking CMAs and CPPs to CQAs
- Obtaining a designated area where the work in the said area results in obtaining a product with a predefined quality
- Control strategy which includes specification of finished products, AS , excipients as well as control over each step of the manufacturing process
- Process capability and its continuous improvement

Fig. 2.11 QbD concept in product development (Jovanovska, 2018).

2.9.4.1 Quality Target Product Profile (QTPP)

Quality Target Product Profile (QTPP) is a prospective summary of product quality characteristics that, if achieved, will result in desired quality, while taking into account the safety and efficacy of the product (ICH, 2009b). QTPP is an indispensable element of the QbD approach and it is the basis for designing a quality, efficient and safe product. For generic products/drugs, QTPP needs to be defined at the onset of development process based on the characteristics of AS, the characterization of the reference product (RP), as well as on the basis of the Summary of Product Characteristics (SPC) and the Patient Information Leaflet (PIL). QTPP includes the following elements: type of dosage form, strength, manner of application, stability, packaging, as well as product quality parameters (identification, content, dissolution, related and degradation products, microbiological purity and residual solvents). Depending on the dosage form, not all of these must be specification parameters. A critical quality parameter (CQA) is the physical, chemical, biological or microbiological property of the output material, i.e. the intermediate or target product that is required to be within the permitted range in order to obtain the product of the desired quality. CQA stems from the pre-set QTPP and is primarily based on the severity of the risk occurrence of a particular damage and does not change as a result of the risk management process (ICH, 2009b).

2.9.4.2 Product design and understanding by establishing a correlation between CMA and CQA

The main objective of designing the product and understanding it is to develop a robust formulation which could deliver the set QTPP within the shelf life of the product. Therefore, the main steps in designing a pharmaceutical product are:

- Physical, chemical and microbiological characterization of AS
- Identification and selection of excipients; type of excipients according to the properties
- Compatibility between AS and excipients
- Optimization of the formulation and identification of critical material attributes (CMA), AS and excipients.

The critical material attributes (CMAs) represent the physical, chemical, biological or microbiological properties of the input material needed to be within the appropriate limits in order to confirm the quality of AS, excipients and the intermediate product. Thereto, CQA of the intermediate product can cross into CMA of the same product, when passing to the next phase of the pharmaceutical-technological process (ICH, 2009b).

Since there are numerous CMAs of AS and excipients that may have an impact on the CQA of the product, they are not all subject to research in the course of the optimization studies. At this stage, a risk assessment is applied in order to prioritize between CMAs from the aspect of their criticality. These will be part of further studies, that is, of the optimization process. Product understanding includes the ability to establish a correlation between CMA and CQA. The steps taken in order to gain an understanding of the product are:

- Identification of all possible CMAs that could affect the quality of the product
- Risk assessment in order to identify CMA with a high level of risk
- Establishing levels of high-risk materials quality parameters
- Perform experiments
- Analysis of the experimental results
- Development of a control strategy for setting acceptable limits for critical quality parameters of work materials.

2.9.4.3 Process design and understanding by establishing a correlation between CPP and CQA

A process parameter is an input operating parameter (mixing rate, mixing time, flow rate of the binding agent, etc.) or a process variable (drying temperature, extrusion pressure of the binding agent, etc.). A critical process parameter (CPP) is a parameter whose variability affects CQA and this is precisely the reason why it should be monitored and controlled in order to ensure a consistent product quality (ICH, 2009b). Accordingly, the state of the process depends on the CPP, but also on the CMA of the input materials. CPP is associated with its effect on product quality and is based on the likelihood of its detection or occurrence, and its criticality can be changed as a result of the risk management process. The purpose of this phase is to design a robust process that will ensure the achievement of a product of desired quality despite the possible variability of input materials and process parameters. Effects of variations in process parameters and materials are examined in robustness studies.

The steps taken in order to gain an understanding of the process are similar with the steps taken to gain understanding of the product and these include:

- Identification of all possible CPP as well as CQA that could affect the quality of the product
- Risk assessment in order to identify CPP with a high level of risk
- Establishing levels of high-risk CPP
- Performing design of experiments (DOE) and determining the design area within which the parameters can vary
- Analyzing experimental results and establishing relationship between CMA, CPP and CQA
- Development of a control strategy for setting acceptable ranges for critical quality parameters of work materials.

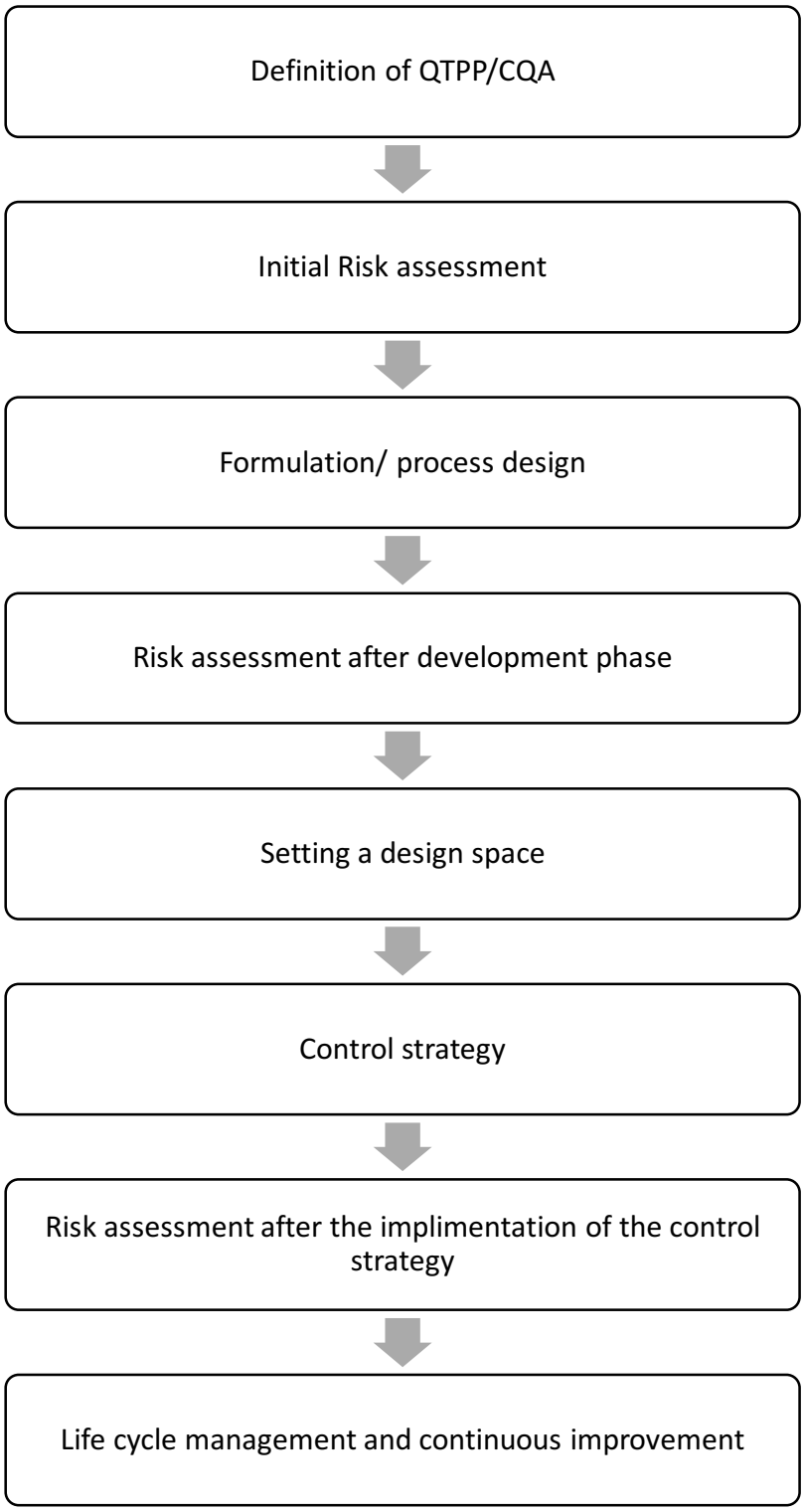


Fig.2.12 Schematic presentation of the implementation of the QbD concept in the product development (Jovanovska, 2018).

2.9.5 QbD implementation tools

2.9.5.1 Product quality risk assessment (Risk Assessment, RA)

The ICHQ9 guide also defines a list of risk assessment tools: basic tools (diagrams, control cards), decision tree, preliminary hazard analysis (PHA), hazard analysis and critical control points (HACP), failure modes and effects analysis (FMEA), failure mode, effects and criticality analysis (FMECA), fault tracking approximator (FTA) for fault detection as well as other auxiliary statistical tools.

2.9.5.1.1 Methods/tools for Risk Assessment (RA)

Product development starts with physicochemical evaluation of an API, which is followed by manufacturing process selection. Parallel to this process is the process of excipient selection – qualitative and quantitative percentage in the formulation. After excipients selection and the manufacturing process, the next challenging step is setting process parameters for every operation of the process.

Prior to development studies, it is necessary to conduct risk assessment of API, excipient selection, manufacturing process selection and process parameters of every operation in order to identify CMA and CPP, which have influence over the CQA. Failure mode effects analysis (FMEA) as a RA tool was used in this PhD thesis.

The goal is to quantify the potential risk of formulation and process variables and assess their impact on drug product manufacturing. Briefly, ranking system covers severity (S), probability (P), and detectability (D) of each parameter. For each factor, scores for S, P, and D are multiplied, yielding a risk priority number (RPN) on a scale from 1 to 64. Any factor with the value of RPN above 30 should be taken into account in further studies (ICHQ9, 2005). This analyze is done using literature and prior knowledge facts. Ranking scale was as follows:

Table 2.6 Ranking scale (Jovanovska, 2018).

Probability (P)	Severity (S)	(Detectability (D)	Ranking
Very unlikely	Minor	Always detected	1
Occasional	Moderate	Regularly detected	2
Repeated	Major	Likely not detected	3
Regular	Extreme	Never detected	4

Table 2.7 Risk classification scale (Jovanovska, 2018).

RPN	Risk classification	Explanation
1-8	LOW	Widely accepted risk No further action is required.
9-30	MEDIUM	The risk is accepted. Further justification is needed in order for the risk to be mitigated
30-64	HIGH	The risk is accepted. Further research is need in order for the risk to be mitigated.

** Probability of the risk can be reduced through DOE optimization

*** Detectability of the risk can be increased through in line PAT system

A relationship between specific quality parameters can be visualized by a fishbone diagram as shown in Figure 3.1. It is important to measure, analyze, and control those factors (CPP, CMA, and CQA) throughout the entire process seamlessly and in real time in order to ensure that products with the target quality are produced (Tho and Bauer-Brandl, 2001)

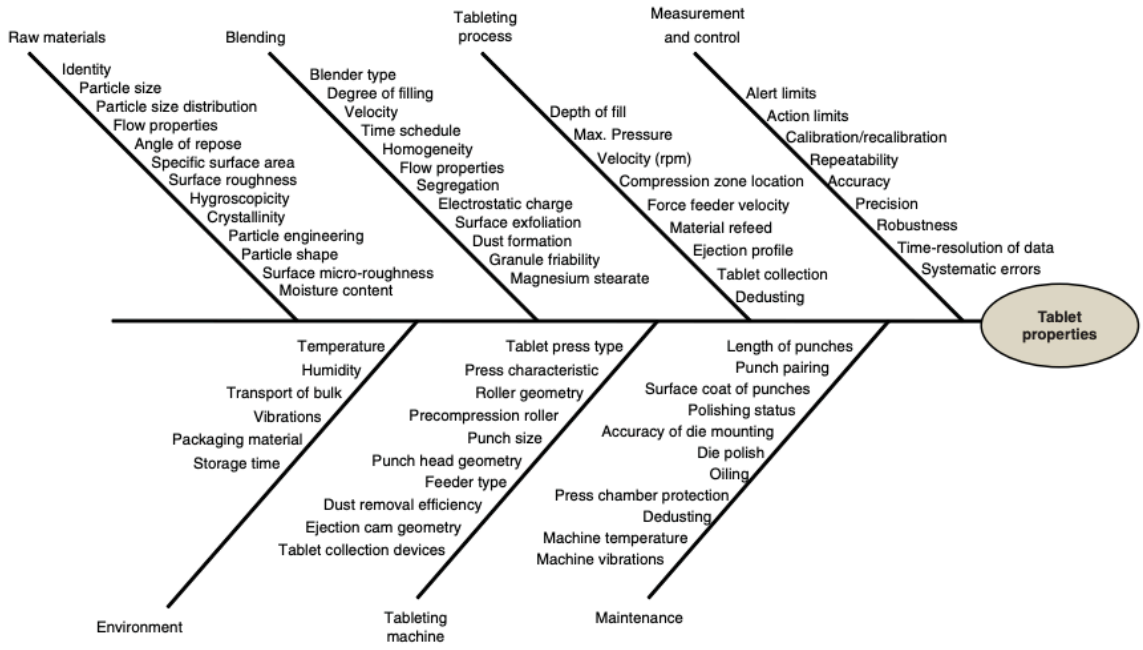


Figure 2.13 Parameters affecting quality target product profile (QTTP) (Tho and Bauer-Brandl, 2001).

2.9.5.2 Design of Experiment (DoE)

A certain derivative risk analysis should be considered before initiating DoE, since factors to be studies during the DoE arise from the said risk analysis. DoE is a structured, organized method for determination of correlations between independent variables/input factors and dependent variables/output within a process (ICH, 2009b). Planning and performing experiments in order to obtain the maximum amount of information from as few experiments as possible is DoE‘s main objective. The basic idea is to vary all the more important factors through a set of planned experiments and then relate and correlate with the results by applying an appropriate mathematical model. Response surface methodology (RSM) belongs to the group of optimization designs that support square models. RSM designs allow response examination across the entire range of variations of the variables and identify the region where the response will have its optimal value. Response surface graphic provides information on the combinations of variables that will give the best desired response. Mixture design is a separate subgroup of the RSM group. Subject of research in these designs

is a mixture composed of several components, the sum of which is 100%. Responses to these designs depend on the relative ratio of the components. Namely, the components cannot be changed independently of one another, due to the fact that the change in one component results in a change of the other components, but the total percentage does not change. Due to this very reason, these designs are useful in optimizing pharmaceutical formulations consisting of multiple components. When applying DoE to formulation/process, CMA and CPP are the input/independent factors while CQA are the output/dependent factors. The application of DoE provides optimal CMA, CPP while providing the design area at the same time.

2.9.5.3 Design Space

As ICH Q8 puts it, design space is "the multi-dimensional combination and interaction of input variables (*e.g.*, material attributes) and process parameters that have been demonstrated to provide assurance of quality". This means that if the manufacturer developed design space with the intended QTPP and it was approved by regulatory organization, he has the liberty to work and play within that space without necessity to notify. On the contrary, if any changes are needed to be done out of the design space an application with these changes should be done and sent to get the approval. First step to implement design space is risk assessment evaluation to reach the QTPP, it's utilized to decide the zone that the risk associated with process is agreeable. Risk assessment has been found to ensure full understanding of any potential risk arising during industry (ICH Q9, 2005).

2.9.5.4 Control Strategy

Several rules taken from product and process understandings that assure the product's and process performance quality is achieved. In QbD methodology the control strategy demand additional realization of the process and product. It involves variables that are associated with drug substance, materials, tools, and in-process controls. Applying control strategy in QbD request additional time and expertise (Aksu

and Mesut, 2015).

2.9.5.5 Process Analytical Technology (PAT)

PAT is a system for design, analysis and control of production process through timely measurements (measurements in progress/during the process) of CQA of raw materials, intermediate products, and process performance parameters, with the goal of ensuring the required final product quality (United States Food and Drug Administration, 2004). PAT is defined as: ―Tools and systems employing real-time measurements or quick measurement taken during the process which include intermediary product performance quality for the purpose of providing information for optimal processing while obtaining a product with the desired quality.

It's a process of assessing. The implementation of PAT could be a section of the control strategy. As stated by FDA, using PAT is crucial to guarantee that the work stays within design space. PAT can lend sustained control on CQAs, CPPs, and CMAs to give the permission for complete process in design space area. Applying PAT to measure attributes online and inline gives the opportunity for discovering defects of the work rather than waiting to assess end-product singly.

After all, the necessity of QbD approach is highly evident nowadays because of noticeable competition between companies to deliver high quality product with cost and time saving methods.

CHAPTER THREE

MATERIALS AND METHODS

3.1 Materials

Ibuprofen DC 85 W, Cellactose® 80 (75% alpha-lactose monohydrate and 25% powdered cellulose), MicroceLac® 100 (75% alpha-lactose monohydrate and 25% microcrystalline cellulose) were kindly donated by BASF (Ludwigshafen, Germany) and Meggle (Wasserburg, Germany) respectively. Magnesium Stearate MF3V1 was purchased from Peter Greven (Germany), Stearic Acid (Sigma Aldrich) and Sodium Stearyl Fumurate (Alubra PG 100) purchased from FMC (Belgium).

3.2 Powder characterization

3.2.1 True density

True density corresponds to the exact volume occupied by the material, without porosity.

Powders were measured by Quantachrome Ultrapyc 1200e Helium pycnometer (Yildiz Technical University, Istanbul, Turkey), using helium to determine the volume of the sample, by measuring the pressure change of helium in a calibrated volume. After sample weight has been specified, apparent particle density is derived automatically (Viana et al., 2002). Values were expressed as the mean of three measurements.

3.2.2 Morphological studies

Particle morphology of API (Ibuprofen DC 85) and both fillers (Cellactose 80 and MicroceLac100) were assessed by Zeiss EVO/LS10 (Yildiz Technical University, Istanbul, Turkey) scanning electron microscopy (SEM). A single layer of powder was attached to metal stubs using double- adhesive carbon tape. Subsequently the powders were sputtered with gold under argon. Images were taken at magnification 250x at an accelerating voltage of 10.00kV.

3.2.3 Flow properties of powders

Flow properties were measured for API, Ibuprofen DC 85 and both fillers (Cellactose 80 and MicroceLac100) individually.

3.2.3.1 Angle of Repose

The angle of repose was determined using the funnel method. (Train 1958, Stanforth 2002).

3.2.3.2 Bulk and tapped densities

An appropriate amount of the sample was poured in a 100 ml tarred graduate cylinder. The cylinder was lightly tapped twice to collect all the powder sticking on the wall of the cylinder. The volume was then read directly from the cylinder and used to calculate the bulk density according to the relationship: mass/volume. Erweka (GMBH SVM 203) tapped density tester was used to measure tapped density according to USP. The volume of the sample was then read and used in the calculation. The bulk and tapped densities were used to calculate the Carr's compressibility index and the Hausner ratio to provide a measure of the flow properties and compressibility of powders (Carr, 1965; Hausner 1967; Shah et al. 2008).

3.3 Study design

3.3.1 QTPP for Ibuprofen tablet formulations

The QTPP is a prospective summary of the quality characteristics of a drug product that ideally will be achieved to ensure the desired quality, taking into account safety and efficacy of the drug product. The QTPP is an essential element of a QbD approach and forms the basis of design of the test product (Chudiwal et al., 2018). QTPP for Ibuprofen tablet formulation was defined early in development based on the properties of the drug substance, desired duration of action and intended patient population (Fig. 3.1).

Table 3.1 Quality Target Product Profile for Ibuprofen tablet formulation

Specification	Target Product Profile
Dosage Form	Immediate Release Tablet (Orally)
Dosage Strength	200 mg
Pharmacological Action	NSAIDs
Tablet weight	400 ≤ weight mg ≥ 404
Weight variation	±5%
Disintegration	Less than 30 minutes in distilled water (ICH)
Dissolution	≥ 80% in 60 minutes
Tensile Strength	1.5MPa
Friability	< 1%

3.4 Selection of model drug

Ibuprofen DC 85W, a non-steroidal anti-inflammatory compound, pre-granulated direct compression product containing 85% of ibuprofen and 15% of excipients, was chosen as a directly compressible model drug for this study in order to understand material behaviour with a compaction simulator (Al-Karawi et al., 2018).

3.5 Formulation Design

In this study, 74 combination formulations were used to evaluate the effect of formulation variables on the quality of Ibuprufen tablets manufactured by direct compression. In order to easily optimize the formulation and evaluate the influence of each excipient on tablet properties, Composing of four variables: Ibuprofen DC 85 W, filler type; Cellactose® 80, MicroceLac® 100, lubricant types that were selected were magnesium stearate (MgSt), Stearic acid (St) and sodium stearyl fumarate (Sf). Lubricant concentrations ranged from 0 to 1.0% as seen in Table 3.2.

Each formulation was prepared by mixing all excipients (except lubricant) manually for 15 minutes. Thereafter adding lubricant and mixing for an additional 5 minutes consistently.

In order to produce any dosage form, a formulation design is usually required. Formulation design constitutes excipients and process formulation.

Table 3.2 Tablet formulation compositions with varying excipient concentrations.

Formulation Code	Ibuprofen DC 85W	Cellactose® 80	MicroceLac® 100	Magnesium Stearate	Stearic Acid	Sodium Stearyl Fumurate	Total Tablet Weight
	(mg)	(mg)	(mg)	(mg/%)	(mg/%)	(mg/%)	(mg)
Ib-0	400	-	-	-	-	-	400
Ib-M1	400	-	-	1(0.25)	-	-	401
Ib-M2	400	-	-	2 (0.50)	-	-	402
Ib-M3	400	-	-	3(0.75)	-	-	403
Ib-M4	400	-	-	4 (1.00)	-	-	404
Ib-St1	400	-	-	-	1(0.25)	-	401
Ib-St2	400	-	-	-	2 (0.50)	-	402
Ib-St3	400	-	-	-	3(0.75)	-	403
Ib-St4	400	-	-	-	4 (1.00)	-	404
Ib-Sf1	400	-	-	-	-	1(0.25)	401
Ib-Sf2	400	-	-	-	-	2 (0.50)	402
Ib-Sf1	400	-	-	-	-	3(0.75)	403
Ib-Sf2	400	-	-	-	-	4 (1.00)	404
Ce-0	-	400	-	-	-	-	400
Ce-M1	-	400	-	1(0.25)	-	-	401
Ce-M2	-	400	-	2 (0.50)	-	-	402
Ce-M3	-	400	-	3(0.75)	-	-	403
Ce-M4	-	400	-	4 (1.00)	-	-	404
Ce-St1	-	400	-	-	1(0.25)	-	401
Ce-St2	-	400	-	-	2 (0.50)	-	402
Ce-St3	-	400	-	-	3(0.75)	-	403
Ce-St4	-	400	-	-	4 (1.00)	-	404

Ce-Sf1	-	400	-	-	-	1(0.25)	401
Ce-Sf2	-	400	-	-	-	2 (0.50)	402
Ce-Sf3	-	400	-	-	-	3(0.75)	403
Ce-Sf4	-	400	-	-	-	4 (1.00)	404
Ml-0	-	-	400	-	-	-	400
Ml-M1	-	-	400	1(0.25)	-	-	401
Ml-M2	-	-	400	2 (0.50)	-	-	402
Ml-M3	-	-	400	3(0.75)	-	-	403
Ml-M4	-	-	400	4 (1.00)	-	-	404
Ml-St1	-	-	400	-	1(0.25)	-	401
Ml-St2	-	-	400	-	2 (0.50)	-	402
Ml-St3	-	-	400	-	3(0.75)	-	403
Ml-St4	-	-	400	-	4 (1.00)	-	404
Ml-Sf1	-	-	400	-	-	1(0.25)	401
Ml-Sf2	-	-	400	-	-	2 (0.50)	402
Ml-Sf3	-	-	400	-	-	3(0.75)	403
Ml-Sf4	-	-	400	-	-	4 (1.00)	404
Ib/Ce-0	200	200	-	-	-	-	400
Ib/Ce-M1	200	200	-	1(0.25)	-	-	401
Ib/Ce-M2	200	200	-	2 (0.50)	-	-	402
Ib/Ce-M3	200	200	-	3(0.75)	-	-	403
Ib/Ce-M4	200	200	-	4 (1.00)	-	-	404
Ib/Ml-0	200	-	200	-	-	-	400
Ib/Ml-1	200	-	200	1(0.25)	-	-	401
Ib/Ml-M2	200	-	200	2 (0.50)	-	-	402
Ib/Ml-M3	200	-	200	3(0.75)	-	-	403
Ib/Ml-M4	200	-	200	4 (1.00)	-	-	404
Ib/Ce-St1	200	200	-	-	1(0.25)	-	401
Ib/Ce-St2	200	200	-	-	2 (0.50)	-	402
Ib/Ce-St3	200	200	-	-	3(0.75)	-	403
Ib/Ce-St4	200	200	-	-	4 (1.00)	-	404
Ib/Ml-St1	200	-	200	-	1(0.25)	-	401
Ib/Ml-St2	200	-	200	-	2 (0.50)	-	402
Ib/Ml-St3	200	-	200	-	3(0.75)	-	403
Ib/Ml-St4	200	-	200	-	4 (1.00)	-	404
Ib/Ce-Sf1	200	200	-	-	-	1(0.25)	401

Ib/Ce-Sf2	200	200	-	-	-	2 (0.50)	402
Ib/Ce-Sf3	200	200	-	-	-	3(0.75)	403
Ib/Ce-Sf4	200	200	-	-	-	4 (1.00)	404
Ib/Ml-Sf1	200	-	200	-	-	1(0.25)	401
Ib/Ml-Sf2	200	-	200	-	-	2 (0.50)	402
Ib/Ml-Sf3	-	-	200	-	-	3(0.75)	403
Ib/Ml-Sf4	-	-	200	-	-	4 (1.00)	404

3.6 Powder blending

All DC grade materials were directly added into the formulations. Three types of lubricants were manually sieved through a #30 sieve (Erweka) before being used in the formulations. Each batch was blended at 25 rpm for 15 minutes without lubricant and blended for 3 minutes after lubricant addition in a cubic mixer (Erweka). The batch size was kept at approximately 200g for each formulation.

3.7 Formation of Compacts

A compaction simulator with cams (Stylcam 200R, Medelpharm, France) and its data acquisition software (Analis, 2.01 version, Medelpharm) were used in this work. This simulator is a single station press with two punch holders. Each punch holder moves with the help of a rotating cam. By design, the upper punch and the lower punch move in a symmetric way during the pre- compression and the compression phases. According to the simulated rotary press, the rotation of the cams is accelerated or slowed down (Celik and Marshall 1989).

Tablets were produced at different compaction forces (5kN and 15kN). Thereafter converted to pressure (MPa), which is calculated as the force exerted per unit area. The forces were measured with strain gauges located on the upper and lower punch holders, with an accuracy of 10N. The accuracy of punches displacement, measured with potentiometric displacement transducers on the punch holders, was 0.01mm. The displacement and the force sampling rates were 5000Hz. Standard Euro B tools with 11.28 mm round, flat-faced punches were fitted on the simulator. Fette

102i rotary press was simulated in this study (Michaut et al., 2010). Tablets were pressed at consistent compaction speed of 10rpm.

The machine deformation (including punch deformation) was taken into consideration during the compression cycles.

Ejection force has been commonly used to evaluate the friction during tableting. Compaction simulator produces ejection force data in order to evaluate the efficiency of the lubricant (Sun, 2015).

Figure 3.1 Compaction Simulator Stylcam 200R

3.8 Determination of QTPP and CQAs for Ibuprofen tablet formulation

Taking into consideration the dosage form and the preparation method selected at the beginning of this analysis, the quality target product profile was initially determined.

From this preliminary study, the CQAs extracted were tensile strength, disintegration time, friability, and ejection force. Measurements of the selected quality attributes were performed on the manufactured tablets.

3.9 Compact characterization (Post-compression parameters)

3.9.1 Weight variation

According to EP, the tablet specimens were weighed individually and had their weights recorded. Then the average weight of the tablets was determined and the % deviation was calculated.

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

(Eq. 3.1)

3.9.2 Friability

Ten tablets were weighed and placed in an Erweka friability tester. The friabi lator was operated for 4 min at 25 rpm, and the friability was then determined after the run as the percent weight loss (Salpekar and Augsburger, 1974).

Figure 3.2 Erweka Friability tester.

3.9.3 Hardness

Tablet hardness (Breaking Force) is the force required to break a tablet. Breaking force of compact was determined by pressing it diametrically using hardness tester (Erweka TBH 225 Series). The apparatus constitutes mainly of two jaws that face each other and one of them usually moves towards the other. each tablet will be placed between the jaws and the force required to break the tablet will be recorded as demonstrate in (Figure 3.3). Mean value and standard deviation was calculated (n=6).

Figure 3.3 Hardness tester.

3.9.4 Thickness

The thickness was measured by automatic caliper (0-150mm TCM) as shown in (Figure 3.4).

Figure 3.4 Automatic Caliper.

3.9.5 Determination of tablet tensile strength

Radial tensile strength of tablets (σ) was obtained from Eqn.(3.2).

$$\sigma = \frac{2F}{\pi.D.h} \qquad \text{(Eq. 3.2)}$$

where F, D, and h are the breaking force, tablet diameter, and thickness, respectively (Paul and Sun, 2018).

Results were shown statistically using mean values ± standard deviation (SD) with n=6 tablets.

3.9.6 In vitro disintegration test

According to USP, the in-vitro disintegration test was carried out using Erweka disintegration tester (Lot# 240 ZT 322). In each tube of the basket-rack assembly, one tablet was placed.

Each tube had a disk added to it. Distilled water, at 37 ± 2°, was used as the immersi on fluid. The time required for the complete disintegration of the tablet was measured until no mass remains in the tube. The disintegration time was determined for three tablets of each formulation, and the mean value and standard deviation were determined (USP35).

Figure 3.5 Disintegration tester.

3.10 Compaction Analysis

Powder compression analysis was made using Compaction simulator Analis software in order to obtain Force-Displacement curves, Force-Time curves and porosity plots.

Powder compression analysis was made using Heckel equation produced by Analis software of compaction simulator. Heckel equation used measured true density values was to calculate in-die yield pressure (Py) values in order to characterize the deformation behavior of materials.

The deformability of the fillers was determined by recording the upper punch pressure and the height of the tablets every millisecond during the compression and decompression cycles (in-die measurements). The yield pressure of the materials was calculated from the reciprocal of the slope of the linear part of the Heckel plot. The

yield pressure calculated by this method has been defined as an apparent yield pressure and is considered to reflect the total deformation of the material, i.e., including both plastic and elastic deformation (Sun and Grant, 2001).

3.11 Data Analysis

The MODDE Pro (Sartorius Stedim Data Analytics) program was used to model the experiments and establish the design space. In MODDE, to understand response factors in more detail, conduct estimations and optimization or find a design space, the quadratic polynomial (model) experiment design is usually examined. Three-level full factorial, central composite, Box Behnken, Onion, and D-Optimal, etc. designs are used for RSM reviews within the program (MODDE, 2018; Suciu et al., 2018).

As seen in Table 3.3, three lubricants were included into the study: magnesium stearate (MgSt), stearic acid (SA), and sodium stearyl fumarate (SSF), as a qualitative input variable; and their ratios were evaluated in the range 0% - 1%, as a quantitative factor. Two fillers, Cellactose® 80 and MicroceLac® 100, were evaluated as a second qualitative factor. The compression pressure, was selected as a quantitative variable and ranged from 5 kN and 15 kN on two levels. A mixture design was generated with 52 runs (Iurian et al. 2020; Wu & Khan 2009); four parameters that resulted from the compaction and tablet quality control analysis were included as responses in the experimental design: tensile strength (MPa), the ejection force (N), the disintegration time (s) of the tablets and their friability (%). A mathematical model for each response was fitted by using the Partial Least Squares (PLS) regression method in the statistical module of the Modde 12.1 Pro software. In addition, through the study, the validity of the experimental design was assessed using a variance test (ANOVA) (Aksu et al. 2012; Betterman et al. 2012).

Table 3.3 Input factors and their levels used for specification in Modde 12.1 Pro software.

Input Factors	Level Settings
Lubricant Type	MgSt; SA; SSF
Lubricant Amount (%)	0; 0,25; 0,5; 0,75; 1
Filler Type	Cellactose® 80; MicroceLac® 100
Compaction Force (kN)	5; 15

3.11.1 Establishment of the design space

The design space is defined by the ICH Q8 as "the multidimensional combination and interaction of input variables (material attributes) and process parameters that have been demonstrated to provide assurance of quality" (Quality by design approach: application of artificial intelligence techniques of tablets manufactured by direct compression. (Aksu et al., 2012) The design space makes QbD a reality, and the broader the design space is to accommodate variations, the more robust and versatile the process is.

3.12 Analytical study for Ibuprofen Optimized Formulations

3.12.1 Assay test

3.12.1.1 Standard preparation

A total of 10 µg/mL standard solution was prepared by dissolving 100 mg of ibuprofen powder in a 100 mL volumetric flask with 0.1 mol/L NaOH solution and making up to volume. Standard solutions of 2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 24µg/ml were prepared using 0.1 mol/L NaOH solution. These prepared dilutions were then analyzed by Shimadzu UV-1800 Spectrophotometer at 221 nm. (Eraga et al. 2015, USP35, 2012). Calibration curve is seen in Figure 3.6.

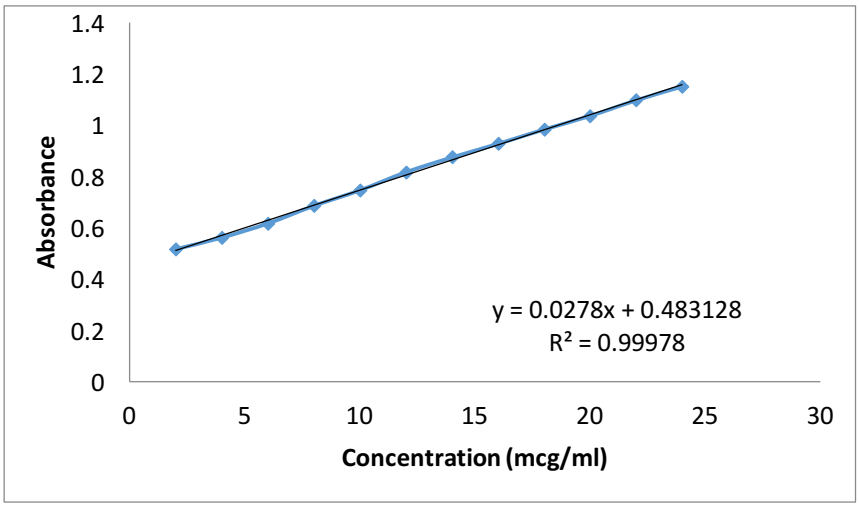


Figure 3.6 Calibration curve for Ibuprofen in 0.1 mol/L NaOH solution.

3.12.1.2 Sample preparation

The average tablet weight of 20 tablets from each optimum formulation (OP1, OP2, OP3,OP4, OP5) was gotten. The tablets were crushed and powder quantity equivalent to 100 mg ibuprofen was dissolved in a 100 mL volumetric flask with 0.1 mol/L NaOH solution and made up to volume. The solution was filtered and 1 mL aliquot of the solution was further diluted to 100 mL to give a 10 µg/mL solution. The absorbance of the resulting solution was read at 221 nm and the percentage content was calculated. (Eraga et al. 2015)

3.12.2 Dissolution studies

3.12.2.1 Calibration curve

Buffer solutions were prepared according to the USP at pH 7.2. The pH was measured using Mettler Toledo pH meter as shown in (Figure 3.7).

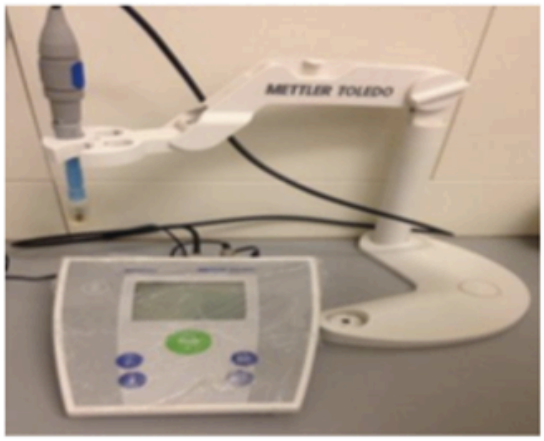


Figure 3.7 Mettler Toledo pH meter.

Figure 3.8 Shimadzu UV-1800 spectrophotometer

For a standard curve of Ibuprofen, stock solution was prepared by dissolving 100 mg of Ibuprofen in 100 ml solvent (phosphate buffer pH 7.2) in a volumetric flask (to get 1000 µg/mL drug solution). 10ml of stock solution was diluted to 100ml with phosphate buffer 7.2 to get a solution containing 100 µg/mL. Standard solutions of 2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 24µg/ml were then prepared using phosphate buffer pH 7.2. These prepared dilutions were then analyzed by Shimadzu UV-1800 Spectrophotometer at 221 nm. (USP 35, 2012) Calibration curve is seen in Figure 3.9.

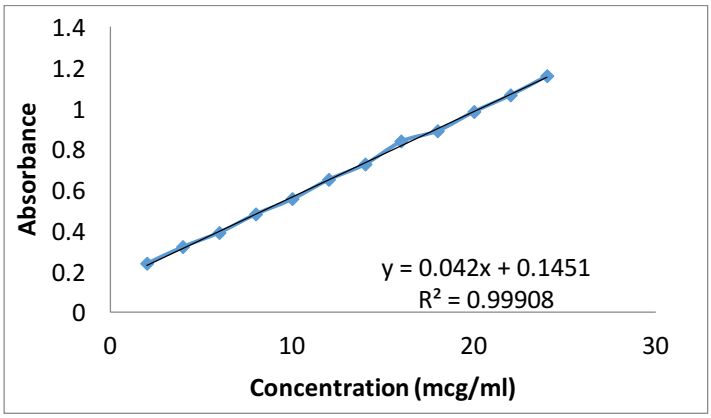


Figure 3.9 Calibration curve for Ibuprofen in pH 7.2 phosphate buffer.

3.12.2.2 Evaluation of Dissolution Profile of Ibuprofen in Optimized Tablet Formulation

Using USP paddle apparatus, dissolution analysis of optimized formulations was performed.

The phosphate buffer (900 mL, pH 7.2, 37°C ± 0.5 °C) was the dissolution m edium. The paddle's rate of agitation was 50 rpm. At predetermined time intervals (after 5, 10, 15, 30, 45, 60 minutes), 3ml was withdrawn. The sampling criteria is stated at specified time intervals, where a specimen will be withdrawn from a midway zone that is between the top of the rotating basket or paddle and the surface of the dissolution medium, provided that it is not less than 1 cm from the vessel wall.

The samples were filtrated using 0,45 μm filter and analyzed using UV spectrophotometry (UV-1700) analysed Ibuprofen at 221 nm after suitable dilution with the phosphate buffer. (Gohel et al., 2007)

The test was conducted using Erweka dissolution tester as shown in (Figure 3.10).

Figure 3.10 Erweka dissolution tester.

3.12.2.3 Similarity (f2) factor calculation

Similarity (f2) factor was calculated for market product (Fourrts) in comparison with optimized formulations. In order to consider the product as similar, it should have an f2 value in the range from (50-100), and the more similar the product is, the higher the value will be.

The similarity (f2) is calculated through the following Equation (3.4):

$$f2 = 50 \cdot \log \{[1+ (1/n)\sum t=1\ n(Rt-Tt)2]-0.5 \cdot 100\} \quad \text{(Eq. 3.4)}$$

In which, Rt and Tt are known as the cumulative percentage dissolved at each selected (n) time points of the reference and test product correspondingly.

3.12.3 Method validation for UV-Vis Spectrophotometer

Validation is a process of establishing documented evidence, which provides a high degree of assurance that a specific activity will consistently produce a desired result or product meeting its predetermined specifications and quality characteristics. The validation for UV method development was performed using parameters like Linearity, Accuracy, Precision, Robustness, and Ruggedness (Behera et al., 2012; Friedrich et al. 2009; Sethuraman & Radhakrishnan, 2013).

3.12.3.1 Linearity

Various aliquots were prepared from the secondary stock solution (100 µg/ml) ranging from 2-24 µg/ml. The samples were scanned in UV-Vis Spectrophotometer.

3.12.3.2 Accuracy

Solutions were prepared in triplicate at levels 80%, 100% and 120% of test concentration using Ibuprofen working Standard as per the test method and taken absorbance of each solution in triplicate. The recovery results showed that the proposed method has an acceptable level of accuracy for Ibuprofen.

3.12.3.3 Precision

Precision of the method was demonstrated by intraday and interday variation studies. In intraday variation study nine different solutions of same concentration were analyzed three times in a day i.e. morning, afternoon and evening. In the interday variation studies, solution of same concentration were analyzed three times for the three consecutive days.

3.12.3.4 Specificity

Spectrum read in the range of 200nm to 400nm for appropriate concentration of sample, blank, and placebo.

3.12.3.5 Robustness

Robustness of the method was determined by carrying out the analysis under different λ-max values.

3.12.3.6 Ruggedness

Ruggedness of the method was determined by carrying out the analysis by different analysts and the respective absorbance was noted (Behera et al., 2012; Friedrich et al. 2009; Sethuraman & Radhakrishnan, 2013).

3.13 Statistical Analysis

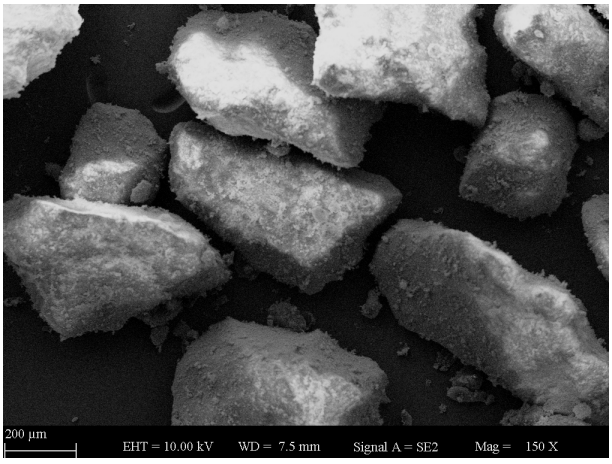
The obtained data are presented as the mean of three experiments ± standard deviation (SD). All of the data was assessed with One-way ANOVA, followed by the Bonferroni multiple comparison test, using GraphPad Prism Software version 6.05VR (La Jolla, USA). P value < 0.05 was considered as the level of statistical significance.

CHAPTER 4

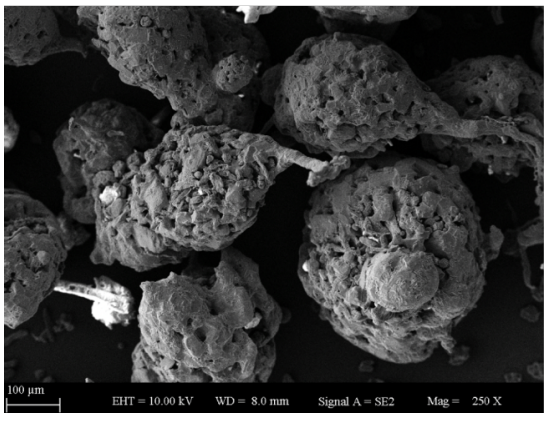
RESULTS AND DISCUSSION

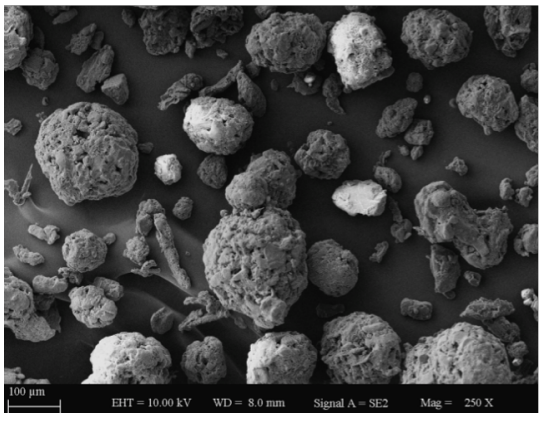
4.1 Powder characterization

Scanning electron microscope (SEM) was used to understand the morphology of the particles for Ibuprofen DC 85, Cellactose® 80, MicroceLac® 100 as seen in figure 4.1. Ibuprofen granules, are seen to be course and have an irregular crystalline structure (figure 4.1a.) in comparison to both fillers; Cellactose® 80 (figure 4.1b.) and MicroceLac® 100 (figure 4.1c.) which are more spherial.



a.





b. **c.**

Figure 4.1 SEM images of the excipients used in this study: (a) Ibuprofen DC 85 (150x), (b) Cellactose® 80 (250x), (c) MicroceLac® 100 (250x).

The SEM images (Figure 4.1) showed a difference between the morphological structure of both co-processed fillers. Cellactose® 80 (Figure 4.1.b.) is composed of long powdered cellulose fibers that are not integrated into the particles therefore having an irregular shape as can be seen in the SEM images. MicroceLac® 100 (Figure 4.1.b.) has more entrapped, shorter fibers of microcrystalline cellulose that incorporate a more spherical form (Meggle, 2020, Mirani, 2011). Cellactose® 80 is seen to have larger particle size as well as a more uneven surface. MicroceLac® 100 is known to have better flowability than Cellactose® 80, which can be explained by it more spherical nature (Meggle, 2020).

Differences in morphological properties, particle size, arrangement and shape of powdered cellulose and MCC leads to differences in compaction behavior of the fillers.

4.2 Flow properties

Bulk and tapped density individual raw materials (Ibuprofen DC 85, Cellactose 80 and MicroceLac 100) were measured and flow characteristics were calculated, the results are presented in Table 4.1.

Table 4.1 Flow properties of powders.

Excipients	Angle of repose (o)	Evaluation based on Angle of repose (o)	Bulk Density (g/cm3)	Tapped Density (g/cm3)	Hausner Ratio	Carr's Compressibility Index (%)	Evaluation based on Carr's Index and Hausner Ratio
Ibuprofen DC 85	27	Excellent	0.54	0.66	1.19	16.52	Fair
Cellactose® 80	35	Good	0.38	0.51	1.31	23.53	Passable
MicroceLac® 100	34	Good	0.51	0.59	1.21	20.65	Fair

*Results were found to be similar to the producers' certificate results.

Bulk and tapped density values for both excipients in formulations didn't show any meaningful differences. The range of bulk density for overall formulations was found to be between 0.44-0.47g/cm3 for Ibuprofen/Cellactose® 80 formulations and between 0.51-0.54g/cm3 for Ibuprofen/ MicroceLac® 100 formulations. The range of tapped density for overall formulations was found to be between 0.56-0.60g/cm3 for Ibuprofen/Cellactose® 80 formulations and between 0.61-0.65g/cm3 for Ibuprofen/ MicroceLac® 100 formulations (Kumar et al. 2009).

4.3 Studies on Ibuprofen DC 85W

4.3.1 Tensile strength

Tablets which were pressed with 50MPa and 150MPa pressure by Compaction simulator were evaluated. Figure 4.2 shows tensile strength results for formulations containing Ibuprofen DC 85 W with different concentrations of magnesium stearate as lubricant (0%, 0.5%, 1%) without inclusion of filler (Roberts et al., 2004).

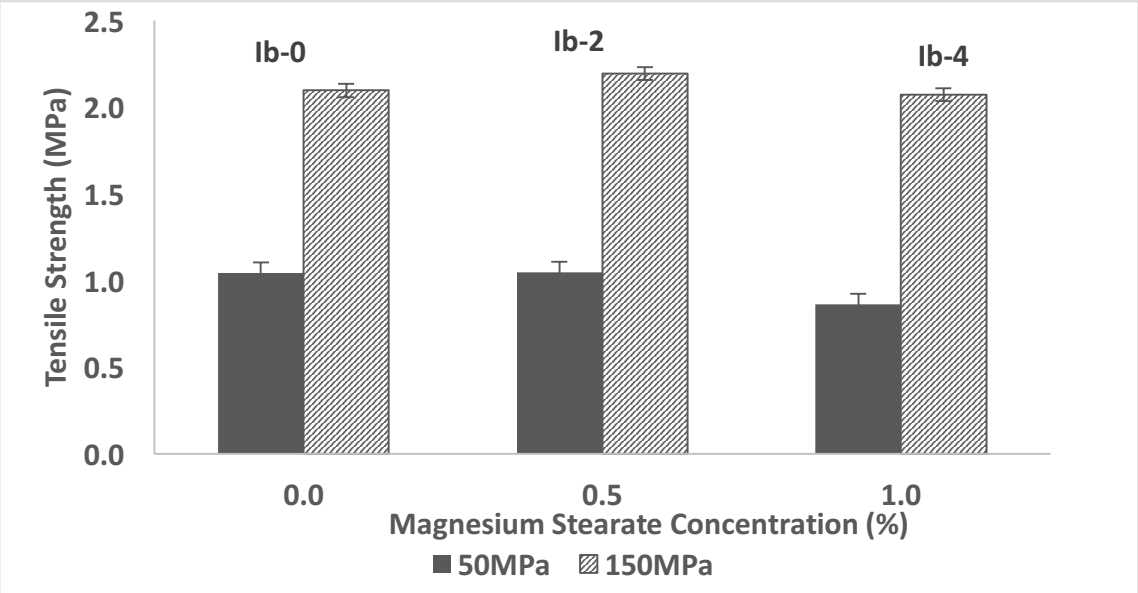


Figure 4.2 Tensile strength results for formulations without filler (Ib-O, Ib-2, Ib-4), compressed at 50MPa and 150MPa pressure. Data are represented as mean ± SD (n=3).

Results show that tablets produced have significance ($p<0.05$) with increased tensile strength at higher compaction pressures (Al-Karawi et al., 2002). This is due to increase in inter-particulate interaction and subsequent improvement in tablet strength (Ruegger and Celik 2000). At 150MPa, tensile strength values ranged from 2.07MPa for Ib-4 and 2.19MPa for Ib-2, indicating Ibuprofen, without addition of filler not significantly affected by change in lubricant concentration.

4.3.2 Ejection force

As seen in Figure 4.3, an increase in MgSt concentration causes a decrease in ejection force, for at both 50 MPa (394N at 0% MgSt Conc. to 282N at 1% MgSt Conc.) and 150MPa (555N at 0% MgSt Conc. to 415N at 1% MgSt Conc.) which is to be expected as seen in previous studies (Paul and Sun, 2018; Sun, 2015). Reduced ejection force reduces wear on punches and makes the tableting process more efficient. Results show that it is possible to press tablets of Ibuprofen DC 85 W, however addition of lubricant without other excipients is not sufficient to reduce ejection force significantly.

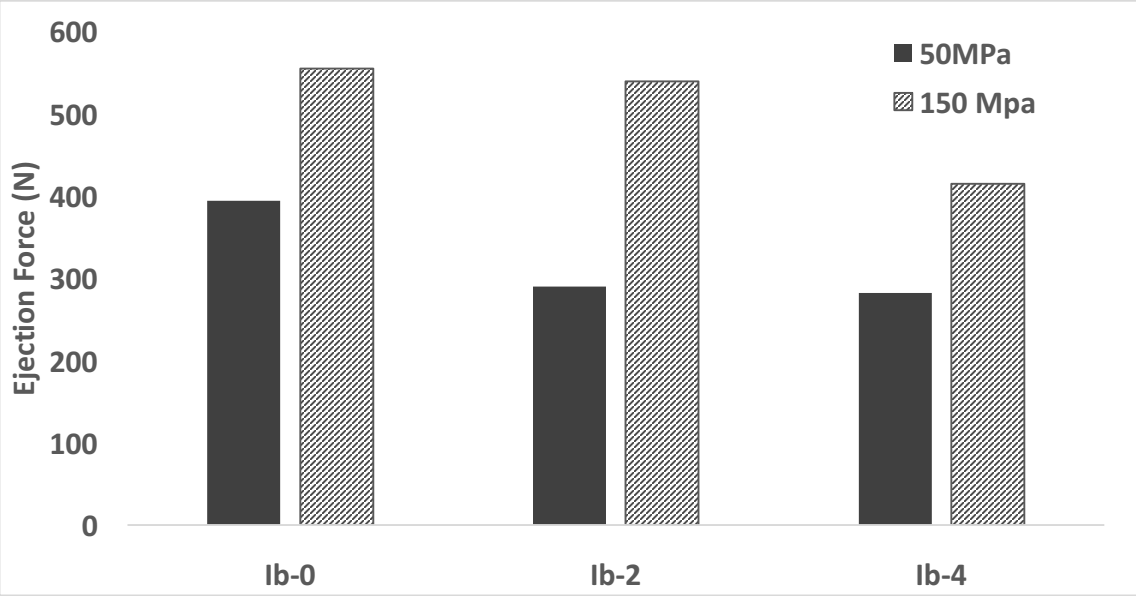


Figure 4.3 Ejection force values for Ibuprofen DC 85W

4.4 Studies on lactose based fillers

4.4.1 Tensile strength

As seen in Figure 4.4; Ce-0, Ce-2, Ce-4 are all formulations containing Cellactose® 80 and Ml-0, Ml-2, Ml-4 contain MicroceLac® 100 with different concentrations of lubricant (0%, 0.5%, 1%). MicroceLac® 100 containing formulations show favorable tensile strength values (0.76-1.13MPa) compared to formulations containing Cellactose® 80 (0.65-0.43MPa) ($p<0.05$). Although not significant, it is also observed, that as concentration of MgSt increases, tensile strength decreases for MicroceLac® 100.

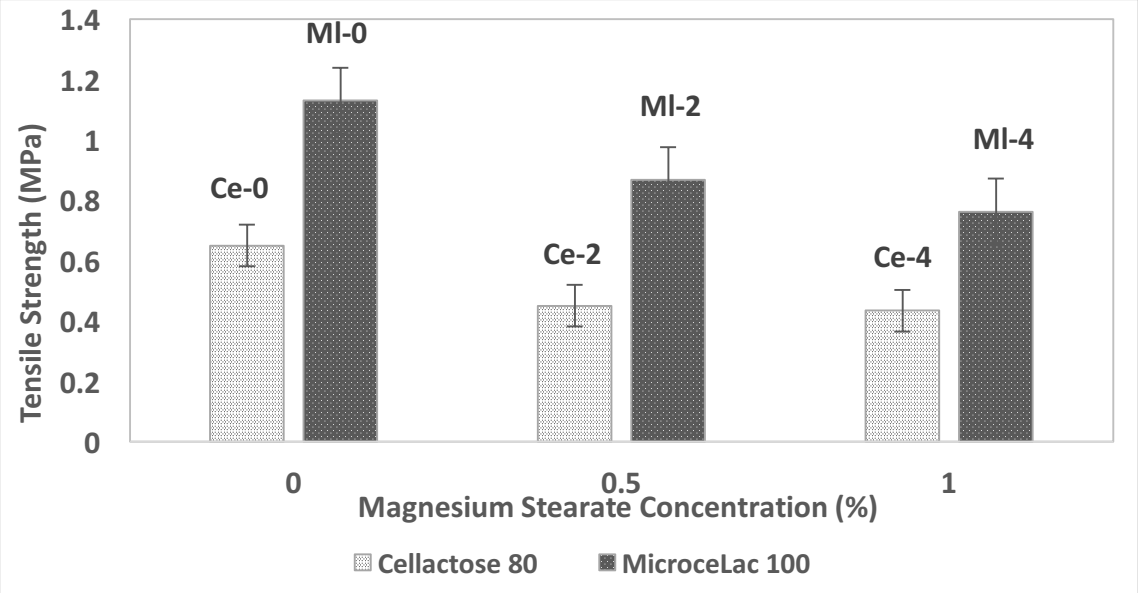


Figure 4.4 Tensile strength values for placebo tablets compressed at 50MPa containing Cellactose® 80 and MicroceLac® 100 at different magnesium stearate concentrations. Data are represented as mean ± SD (n=3)

Tensile strength results (Figure 4.2 and Figure 4.4) are concurrent with previous studies done. It shows an increase in lubrication concentration causes negative effect on tablet strength. This is dependent on the attractive forces and contact between particles over the entire contacting area. Eventual tablet strength is affected

by the fine lubricant particles interfering with the interactive bonding forces between particles. The negative effect of MgSt has more impact on plastically deforming materials. (Arida and Al-Tabakha, 2008; Dudhat et al., 2017; Wang et al., 2010)

4.4.2 Ejection force

Figure 4.5 shows measured ejection force values produced by Compaction Simulator. A high ejection force is indicative of high friction at the tablet–die wall interface. Excessive friction can damage tablet and reduce tooling life by wearing. Pure, unlubricated Cellactose® 80 shows overall decreased ejection force compared too unlubricated MicroceLac® 100. A previous study showed that ejection tends to decrease more rapidly with increasing compaction pressure for materials with lower yield pressure (Sun, 2015). This is concurrent with results of the study, showing Cellactose® 80 (Py-116.6MPa) with reduced ejection force in comparison with MicroceLac® 100 (Py-122.4MPa).

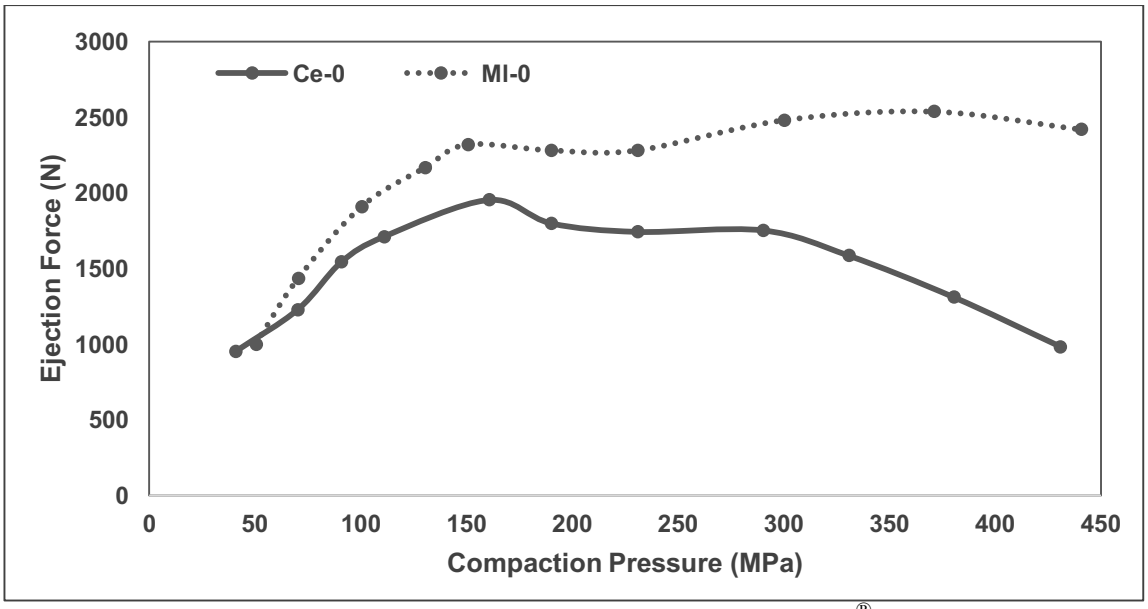


Figure 4.5 Comparison of ejection force data of Cellactose® 80 (Ce-O) and MicroceLac® 100 (Ml-O) Data are represented as mean ± SD (n=3)

4.4.3 Force-Displacement curve

Table 4.2a and 4.2b show energy values for both fillers pressed at various compaction forces (5-43kN). As seen, there is no significant difference between total energy values for both fillers.

Figure 4.6 and 4.7 show Force displacement plots for pure fillers at compaction forces varying from 5-45kN. The area under the curve corresponds to energy. As seen, increase in compaction pressure caused an increase in total energy for both formulations as seen in a previous studies (De Blaey &Polderman, 1971; Ragnarsson & Sjögren, 1985; Tay et al., 2019).

Table 4.2a Data of Energy produced from compaction simulator for pure Cellactose® 80 at varying compaction forces.

Compaction force (kN)	Rearrangement Energy (J)	Compression Energy (J)	Flow Energy (J)	Elastic Energy (J)	Plastic Energy (J)	Ejection Energy (J)	Total Energy (J)
5.03	26.166	3.886	0.06	-0.036	3.85	3.139	37.065
7.58	40.961	5.507	0.113	-0.04	5.467	3.948	55.956
10.23	56.798	7.168	0.147	-0.056	7.112	4.352	75.521
12.47	71.084	8.253	0.197	-0.052	8.201	4.664	92.347
16.83	99.372	10.422	0.215	-0.08	10.342	4.847	125.118
20.15	121.422	11.849	0.194	-0.113	11.736	4.72	149.808
24.03	148.668	13.411	0.145	-0.167	13.244	5.095	180.396
28.8	182.551	14.971	0.096	-0.366	14.604	6.338	218.194
33.04	212.815	16.282	0.107	-0.63	15.651	6.025	250.25
37.24	244.337	17.683	0.047	-0.898	16.785	5.425	283.379
41.73	280.604	18.826	0.053	-1.409	17.417	5.714	321.205

Table 4.2b Data of Energy produced from compaction simulator for pure MicroceLac® 100 at varying compaction forces.

Compaction force (kN)	Rearrangement Energy (J)	Compression Energy (J)	Flow Energy (J)	Elastic Energy (J)	Plastic Energy (J)	Ejection Energy (J)	Total Energy (J)
5.67	29.453	4.287	0.102	-0.023	4.264	3.356	41.439
7.89	42.324	5.82	0.127	-0.032	5.788	4.413	58.44
10.94	60.592	7.662	0.182	-0.036	7.626	5.704	81.73
13.8	79.452	9.207	0.184	-0.053	9.153	5.993	103.936
16.51	97.541	10.493	0.218	-0.059	10.434	6.42	125.047
19.22	116.566	11.69	0.196	-0.086	1.605	6.215	136.186
23.83	147.796	13.578	0.194	-0.105	13.473	6.753	181.689
29.79	190.761	15.43	0.154	-0.296	15.134	6.751	227.934
36.74	241.424	17.713	0.048	-0.733	16.981	7.416	282.849
42.5	286.112	19.512	0.05	-1.335	18.177	7.996	330.512

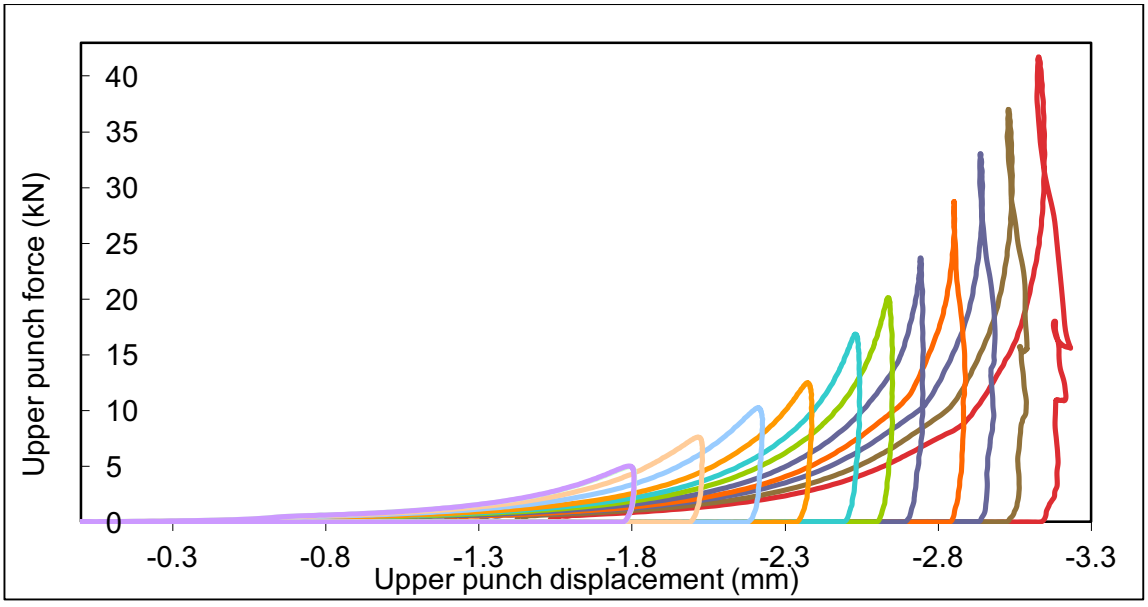


Figure 4.6 Compression cycles (force–displacement curves) for pure Cellactose® 80 from 5-45kN compaction force.

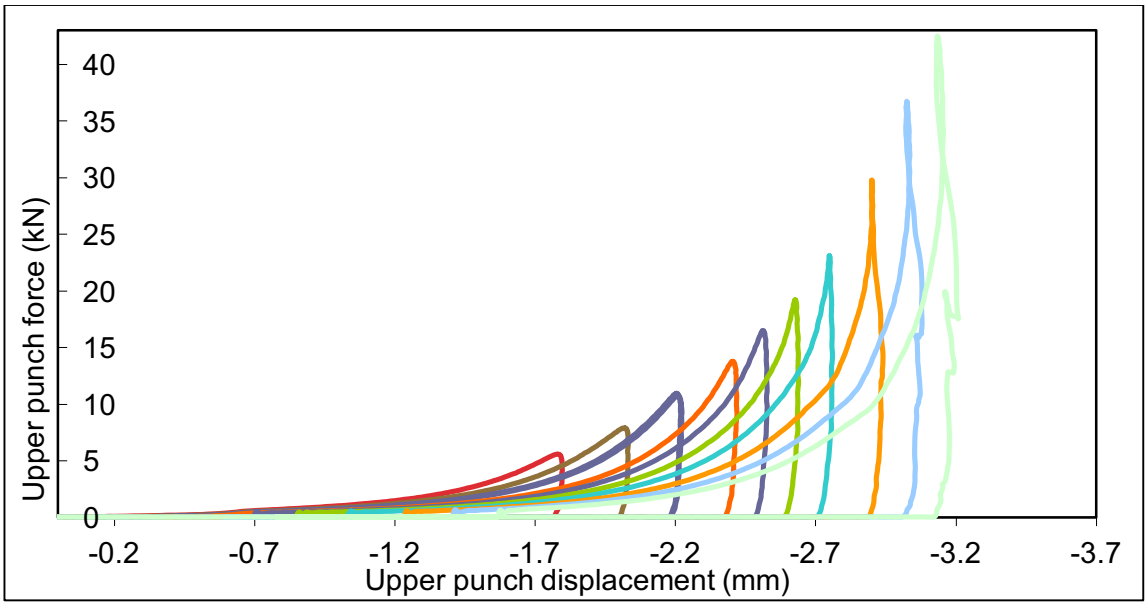
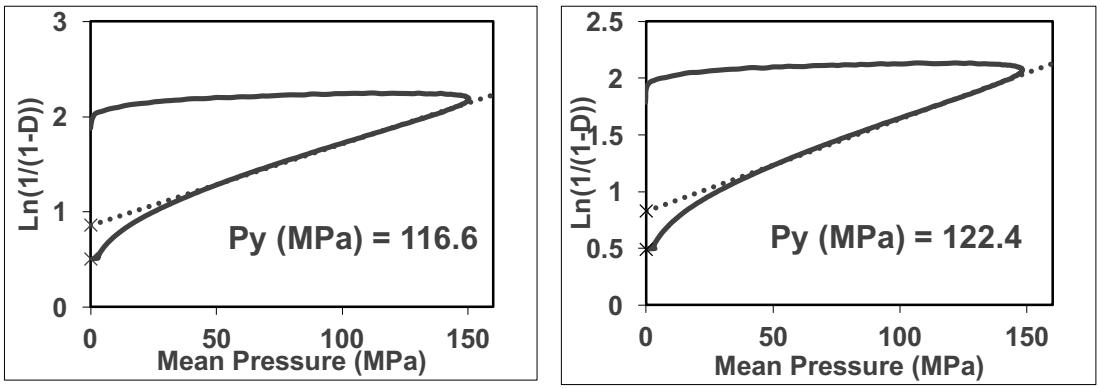


Figure 4.7 Compression cycles (force–displacement curves) for pure MicroceLac® 80 from 5-45kN compaction force.

4.4.4 Heckel Analysis

Important material properties particularly Yield pressure (Py) is calculated from the linear slopes k in order to characterize the deformation behavior of materials. As seen in Figure 4.8, pure unlubricated Cellactose® 80 (Py-116.6MPa), containing powdered cellulose component is more plastically deforming in comparison to pure unlubricated MicroceLac® 100 (Py-122.4MPa) containing microcrystalline cellulose component as seen by lower Py value (Py-116.6) (<0.5 significance). Differences in powder composition, lead to differences in deformation mechanisms as well as tablet strength (Onayo et al., 2020; Sun and Grant, 2001).



(a) Cellactose® 80 (b) MicroceLac® 100

Figure 4.8 Heckel plots for two fillers (a) and (b) produced by compaction simulator at 150MPa pressure.

4.4.5 Effect of compaction pressure on porosity of the compact

During powder densification, the porosity of a powder bed decreases. Figure 4.9 reflects the porosity load of pure Cellactose® 80 and MicroceLac® 100 with increasing compression pressure. For all powders, tablet porosity decreased with increasing compaction pressure in a non-linear way. However, the compaction pressure for obtaining zero porosity varied between the materials. Zero porosity is achieved at 382MPa for pure Cellactose® 80 and 446MPa for pure MicroceLac® 100. (Newton and Grant, 1974; Nordström et al. 2013).

The yield pressure (Figure 4.8) of the two single materials illustrates the difference in densification behaviour as seen in Figure 4.9. As reported previously, MicroceLac® 100 (Figure 4.8.b) has a higher yield pressure than Cellactose® 80 (Figure 4.8.a). The high yield pressure of MicroceLac® 100 explains its difficult densification. The figure shows that the second component; Cellactose® 80, with lower yield pressure has enhanced densification, this results in a lower porosity under pressure. (Cook & Summers, 1990; Duberg and Nyström, 1985; Van der Voort Maarschalk et al., 1999; Van Veen et al., 2000)

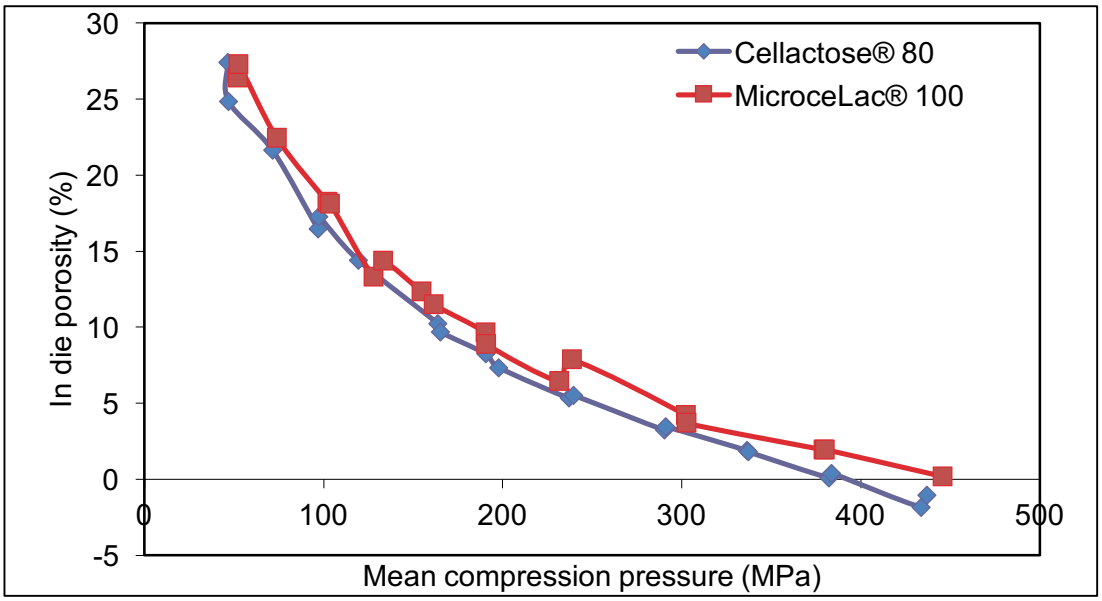


Figure 4.9 In die porosity (%) of pure Cellactose® 80 and MicroceLac® 100 at compression pressures between 5MPa and 450MPa

4.5 Studies on combination formulations

4.5.1 Force-Time curve

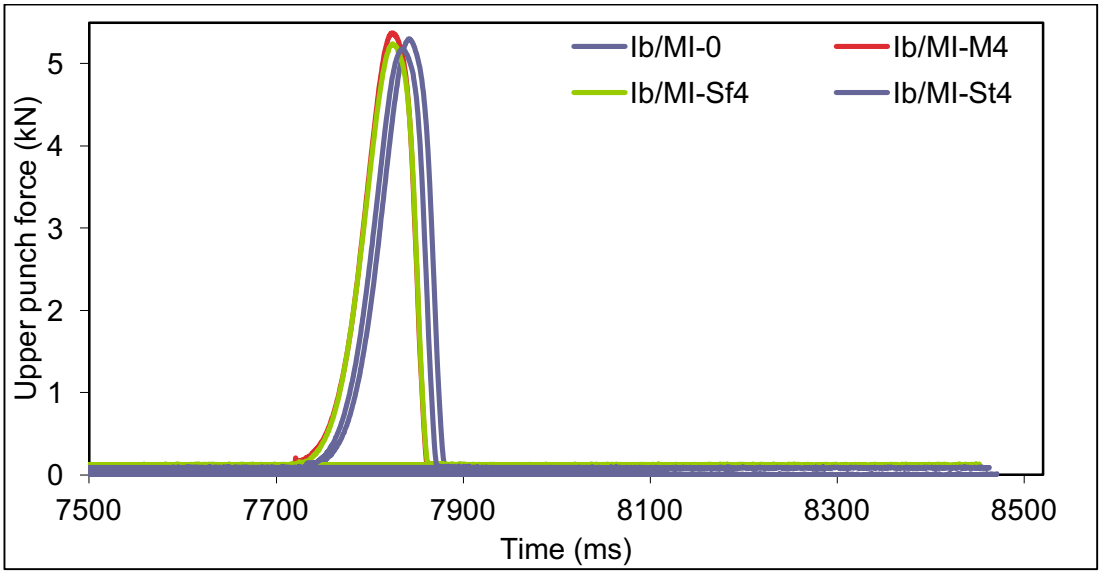


Figure 4.10 Force-Time curve for MicroceLac® 100 containing formulations at 5kN compaction force.

Figure 4.10 shows the Force-time curve for combination formulations containing MicroceLac® 100 as a filler with 1% lubricant (Magnesium Stearate, Stearic Acid, Sodium Stearyl Fumurate) concentrations. All tablets were pressed with a compaction speed of 10rpm (Leitritz et al., 1996; Yliruusi, 1997).

4.5.2 Post compaction data

Table 4.3 Results for combination formulations

Tablet combination formulations	Compaction Force (kN)	Tensile Strength (Mpa)	Disintegration (s)	Friability (%)	Ejection Force (N)
Ib/Ce-0	**5**	0.488	12	2.332	281
Ib/Ce-0	**15**	1.985	109	0.520	498
Ib/Ce-1	**5**	0.463	14	2.367	226
Ib/Ce-1	**15**	1.854	269	0.492	305
Ib/Ce-M2	**5**	0.504	10	2.473	149
Ib/Ce-M2	**15**	2.019	256	0.620	324
Ib/Ce-M3	**5**	0.554	12	2.456	142
Ib/Ce-M3	**15**	2.013	255	0.684	285
Ib/Ce-M4	**5**	0.453	13	2.142	80
Ib/Ce-M4	**15**	1.700	314	0.732	305
Ib/Ml-0	**5**	0.682	12	1.289	330
Ib/Ml-0	**15**	2.418	255	0.526	501
Ib/Ml-1	**5**	0.748	12	1.404	156
Ib/Ml-1	**15**	2.470	233	0.545	353
Ib/Ml-M2	**5**	0.702	12	1.656	193
Ib/Ml-M2	**15**	2.629	231	0.626	307
Ib/Ml-M3	**5**	0.616	14	1.582	147
Ib/Ml-M3	**15**	2.304	234	0.644	276
Ib/Ml-M4	**5**	0.636	15	1.424	171
Ib/Ml-M4	**15**	2.304	256	0.673	297
Ib/Ce-St1	**5**	0.422	10	2.365	244
Ib/Ce-St1	**15**	1.922	162	0.723	514
Ib/Ce-St2	**5**	0.366	12	2.473	213
Ib/Ce-St2	**15**	2.076	166	0.765	506
Ib/Ce-St3	**5**	0.346	14	2.335	192
Ib/Ce-St3	**15**	2.008	155	0.744	452
Ib/Ce-St4	**5**	0.371	18	2.456	175

Ib/Ce-St4	**15**	2.099	127	0.616	349
Ib/Ml-St1	**5**	0.631	15	1.588	243
Ib/Ml-St1	**15**	2.276	167	0.678	515
Ib/Ml-St2	**5**	0.763	16	1.582	241
Ib/Ml-St2	**15**	2.413	217	0.598	450
Ib/Ml-St3	**5**	0.616	18	1.290	246
Ib/Ml-St3	**15**	2.458	174	0.604	467
Ib/Ml-St4	**5**	0.697	18	1.346	283
Ib/Ml-St4	**15**	2.333	190	0.553	491
Ib/Ce-Sf1	**5**	0.412	10	2.332	254
Ib/Ce-Sf1	**15**	2.185	169	0.794	391
Ib/Ce-Sf2	**5**	0.519	13	2.459	182
Ib/Ce-Sf2	**15**	2.190	207	0.699	317
Ib/Ce-Sf3	**5**	0.473	15	2.584	115
Ib/Ce-Sf3	**15**	2.373	293	0.665	295
Ib/Ce-Sf4	**5**	0.366	12	2.491	110
Ib/Ce-Sf4	**15**	1.962	271	0.785	285
Ib/Ml-Sf1	**5**	0.570	13	1.550	216
Ib/Ml-Sf1	**15**	2.658	286	0.695	320
Ib/Ml-Sf2	**5**	0.529	15	1.357	192
Ib/Ml-Sf2	**15**	2.493	280	0.598	308
Ib/Ml-Sf3	**5**	0.417	13	1.347	150
Ib/Ml-Sf3	**15**	2.664	320	0.670	284
Ib/Ml-Sf4	**5**	0.554	17	1.658	142
Ib/Ml-Sf4	**15**	2.595	298	0.694	268

Table 4.3 shows results of for tablet combination formulations. It can be see that increase in compaction force has an overall positive impact on tensile strength and friability, however a negative impact on disintegration. Increase in compaction force also caused increase in ejection force (Salpekar and Augsburger, 1974; Sun, 2015).

4.5.2.1 Friability

Friability results shown in table 4.3 prove that 5kN compaction force is not enough to pass Pharmacopeia requirements of >1%. However, tablets pressed at 15kN all passed friability test.

4.5.2.2 Tensile Strength

Figure 4.11 below shows the Tensile strength of combination formulations pressed at 150MPa compaction pressure, for different lubricant concentrations. As an overall trend, most formulations had reduced tensile strength values at 1% lubricant with exception of Ib/MI-Sf. Proving the negative effect of lubricant on tensile strength in formulations. Overall, Cellactose® 80 containing formulations had lower tensile strength than MicroceLac® 100 which is concurrent with previous studies (Arida and Al-Tabakha, 2008; Dudhat et al. 2017; York & Pilpel, 1973).

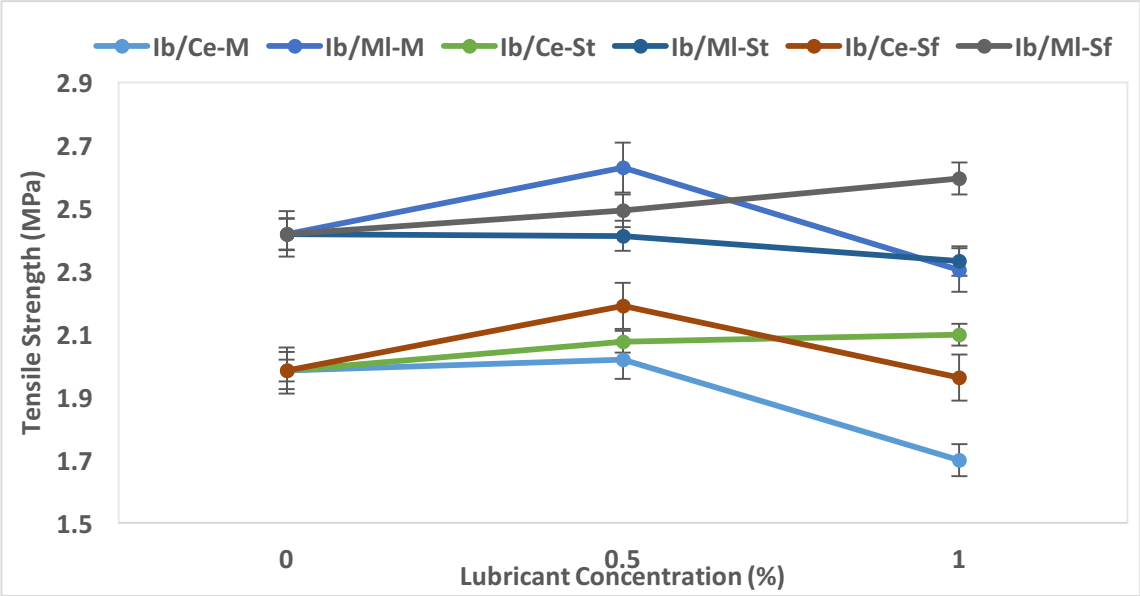
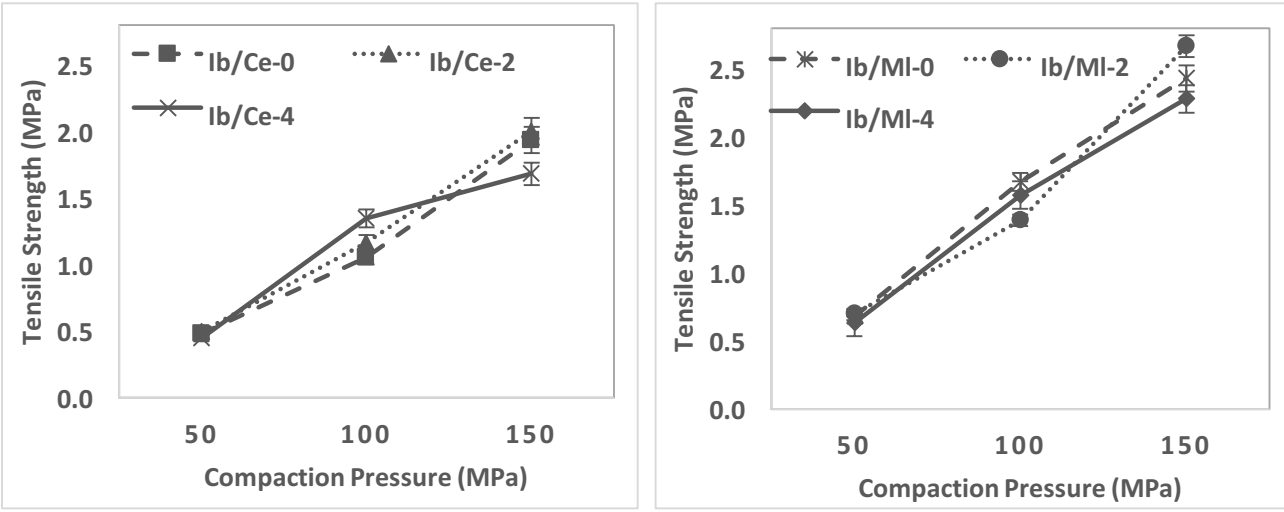


Figure 4.11 Tensile strength for combination formulations at 150MPa compaction pressure

Figure 4.12 shows combination formulations containing Cellactose® 80 (Ib/Ce-0, Ib/Ce-2, Ib/Ce4) and MicroceLac® 100 (Ib/Ml-O, Ib/Ml-2, Ib/Ml-4). It is observed, in agreement with the above results, that MicroceLac® 100 containing formulations have overall higher tensile strength in comparison with Cellactose® 80. Significant differences are seen at higher compaction pressure (150MPa). Similar study done by Muzíková, and Zvolánková (2007) show concurrent results that the strength of the compacts from pure Cellactose® 80 was lower than that of those from

MicroceLac® 100 both with and without the addition of lubricant. Results confirm differences due to composition and morphology which is seen in SEM images (Figure 1). Smooth particles tend to have high surface to mass ratio which make them more cohesive. Coarse particles are more influenced by gravity forces which make it less cohesive, leading to lower tensile strength (Edge et al., 2000).



a *b*

Figure 4.12 Tensile strength values for formulations containing Ibuprofen DC 85 W, Cellactose® 80 / MicroceLac® 100 and different MgSt concentrations at different pressures.

Data are represented as mean ± SD (n=3)

4.5.2.3 Disintegration

Compaction force greatly affects disintegration time as widely known. Increase in compaction force caused increase in disintegration time as seen in Table 4.3. (Khan and Rhodes, 1976). Overall, disintegration time is not seen to be significantly affected by the type of filler, the type or concentration of lubricant. At 15kN compaction force, Ib/Ce-0 (containing Cellactose as filler and no lubricant) had the fastest disintegration time (109 seconds) while the slowest disintegration time was Ib/MI-Sf3 which contained MicroceLac as filler with 0.75% Sodium Stearyl Fumurate as lubricant.

4.5.2.4 Ejection force

Reduced ejection force reduces wear on punches and makes the tableting process more efficient.Figure 4.10 shows the effect of lubricant type and concentration on ejection force of Cellactose® 80 containing formulations. Overall, Cellactose® 80 showed lower ejection force values in comparison to MicroceLac® 100. As widely known, increase in lubricant concentration reduces ejection force which is concurrent with results in this study (Khan & Rhodes 1976; Paul and Sun, 2018; Sun, 2015). as seen in Figure 4.13 and Figure 4.14. For both fillers, Sodium stearyl fumurate is seen to have the least effect on reducing ejection force. Both Magnesium Stearate and Stearic acid succeeded in reducing ejection force significantly with increase in concentration.

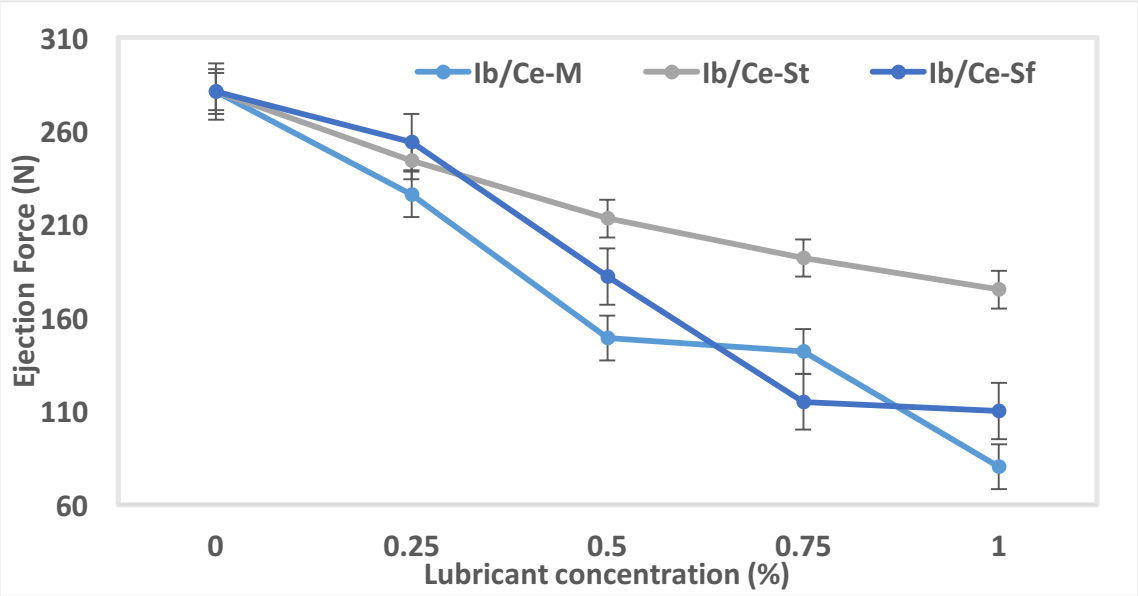


Figure 4.13 Ejection force for Cellactose® 80 formulations with different lubricant types and concentrations at 50MPa compaction pressure.

Lubricant concentration effect on ejection force for all combination formulations is seen in Figure 4.13 and 4.14 (Khan & Rhodes 1976; Paul & Sun 2018; Sun 2015). Formulations containing pure Cellactose® 80 show decreased ejection

force compared to pure MicroceLac® 100 (as seen in Figure 4.5), however, differences observed are not as prominent when in combination with Ibuprofen DC 85 W.

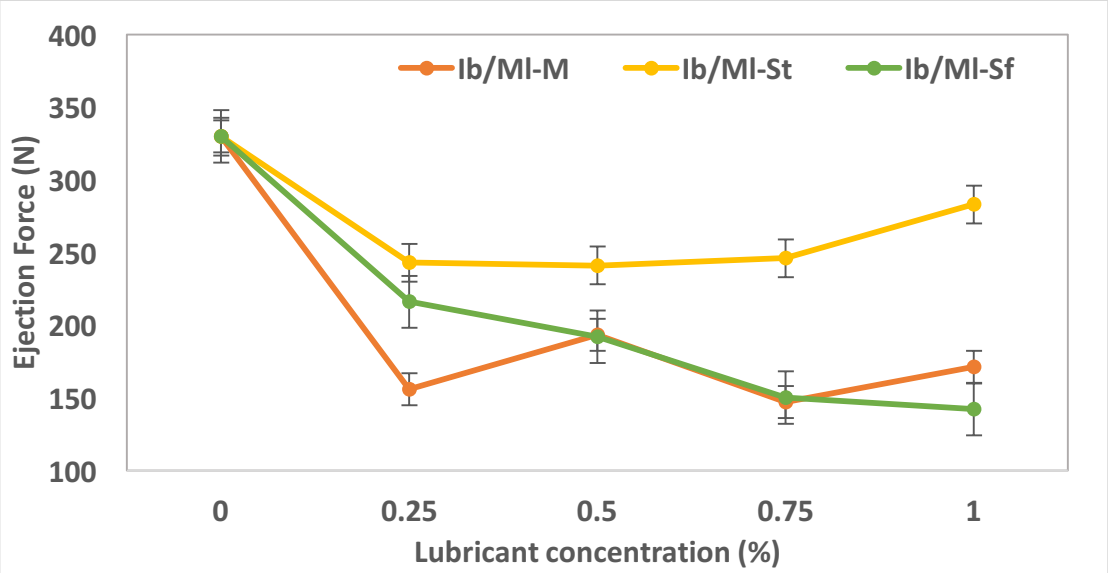


Figure 4.14 Ejection force for MicroceLac® 100 formulations with different lubricant types and concentrations.

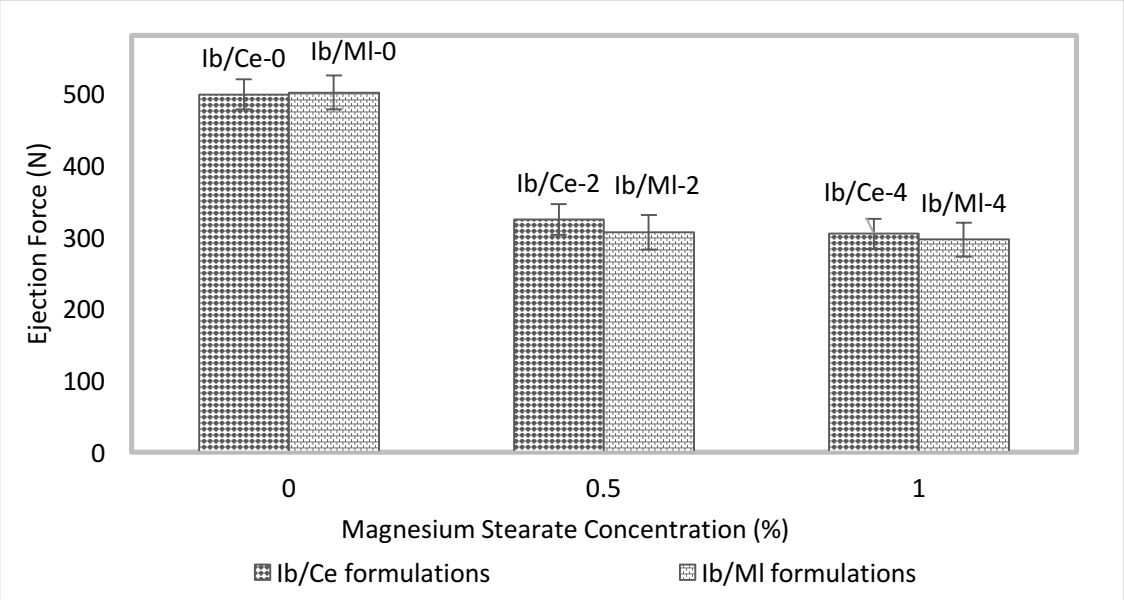


Figure 4.15 Comparison of ejection forces for formulations compressed at minimum pressure(50MPa). Data are represented as mean ± SD (n=3)

Different behavior of fillers is due to the variance in the composition and particle characteristics as seen in SEM results (Figure 4.1b and 4.1c.). Figure 4.15 shows that an increase in MgSt concentration causes a decrease in ejection force, for both Cellactose® 80 (498N at 0% MgSt Conc. to 304N at 1% MgSt Conc.) and MicroceLac® 100 (501N at 0% MgSt Conc. to 296N at 1% MgSt Conc.) which is to be expected as seen in previous studies (Paul and Sun, 2018; Sun and Grant, 2015). Ejection force values indicate that 0.5% MgSt is efficient in this formulation, as an increase in MgSt concentration to 1% does not improve ejection force values significantly.

As a result, the characteristics of the fillers may serve as a useful tool in evaluating their effectiveness and formulation efforts. An attempt was made to observe the differences in the behaviour of two fillers in combination with model drug Ibuprofen DC. The obtained data supports that the selection of fillers affects the compressibility of formulations. Addition of filler improves the efficiency of compression by reducing ejection force and increasing robustness of formulation.

4.6 Quality by Design

4.6.1 Quality Target Product Profile (QTPP) and Critical Quality Attriutes (CQAs) for Ibuprofen tablet formulation

The quality target product profile was initially defined taking into consideration the dosage form and the preparation method, which was selected at the beginning of this study. The CQAs derived from this preliminary analysis were tensile strength, disintegration time, friability and ejection force. Measurements of the selected quality attributes were performed on the manufactured tablets.

4.6.2 Results of data Analysis

4.6.2.1 Model Evaluation

The validity of the experimental design was checked by the analysis of variance (ANOVA) test. According to ANOVA, a model with R^2 (coefficient of

determination) of 0.5 is a model with rather low significance. Q^2 (predictive power of the model) should be greater than 0.1 for a significant model and greater than 0.5 for a good model. The difference between R2 and Q2 should also be smaller than 0.3 for a good model. Q2 is the best and most sensitive indicator (Sucui et al., 2018). As seen in Figure 4.13, a significant model were created for each attribute.

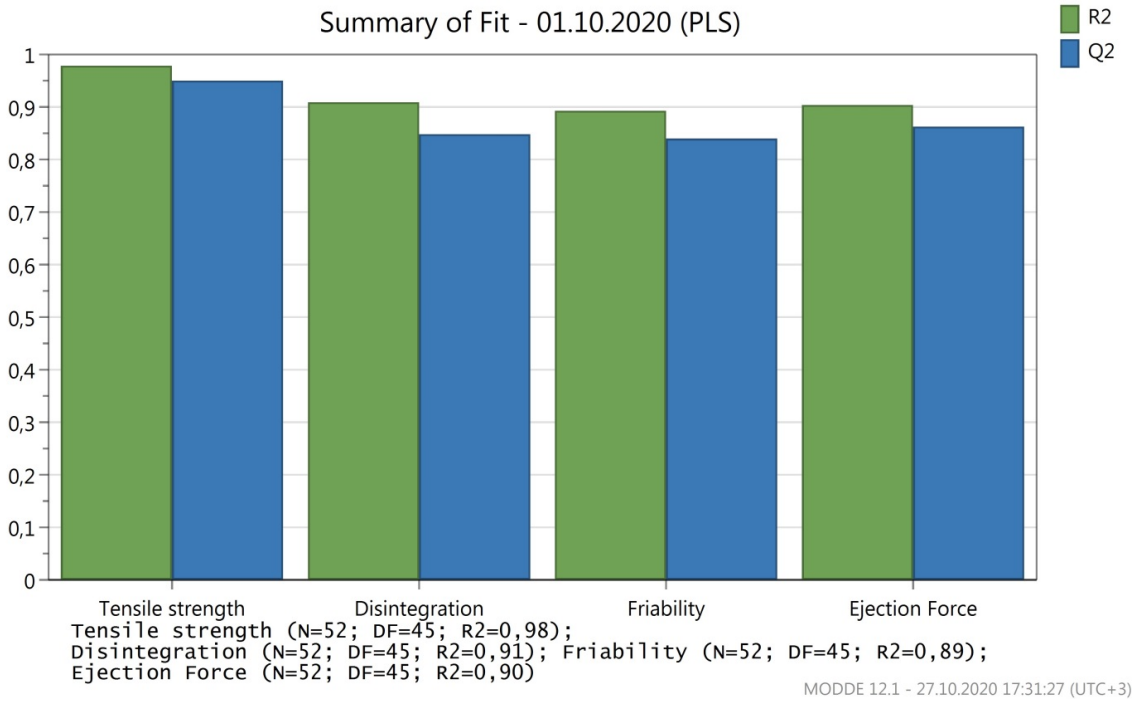


Figure 4.16 Summary of Model fit according to ANOVA test.

The revised values of the model equation's regression coefficients are present ed as histograms (Figure 4.17-4.20). In order to determine their significance and show the magnitude of the effects of variables on the responses, the coefficient plot presents a graphical representation of the model terms, while their sign indicates a positive or a negative impact 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 (Barimani et al. 2018; Casian et al. 2017; Lurian et al. 2020; Nie et al. 2018; Suciu et al. 2018; Taipale-Kovalainen et al. 2018).

According to model fitting results, Compaction force shows significant effect on each response with accordance to previous knowledge of studies (Al-Karawi et al., 2018; Roberts et al., 2004; Ruegger and Celik, 2000).

4.6.2.1.1 Tensile Strength Modde Analysis

Filler type models show notable effect on tensile strength(TS). However, the lubricant type doesn't show significant effect on tensile strength as seen due to uncertainty level not extending across y=0. As well-known, compaction force shows great effect on tensile strength; increase in compaction force is known to increase tensile strength for all formulations (Al-Karawi et al., 2018; Roberts et al., 2004; Ruegger and Celik, 2000).

Overall, Fil (B) (MicroceLac® 100) containing formulations are seen to have an enhancing effect on TS as seen by the positive bar in figure 4.17. Where Fil (A) (Cellactose® 80) is seen to have a mitigating effect on TS as seen below.

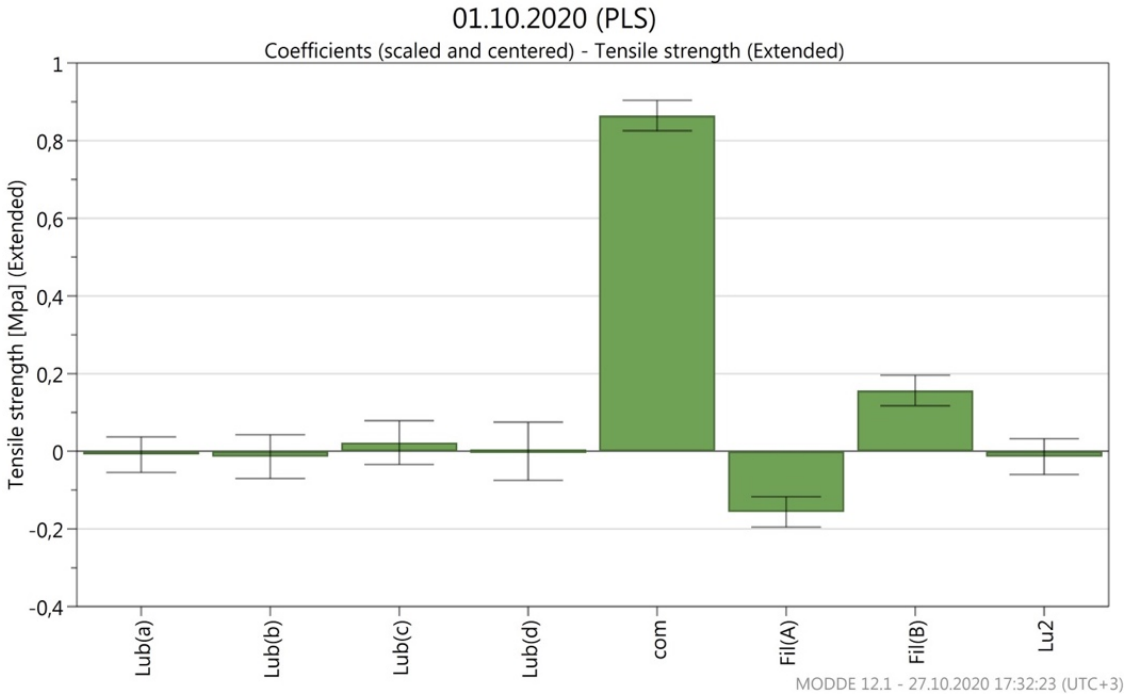


Figure 4.17 Overview plots for model evaluation of Tensile Strength and the values of the regression coefficients of the model equations.

4.6.2.1.2 In vitro disintegration test Modde Analysis

The disintegration times ranged between 10 Seconds to 5.3Minutes. Figure 4.18 shows that disintegration time was not significantly influenced by filler type or lubricant type and amount. However, was greatly influenced by compaction force as widely known. Increase in compaction force caused increase in disintegration time (Khan and Rhodes, 1976; Schiermeier and Schmidt, 2002).

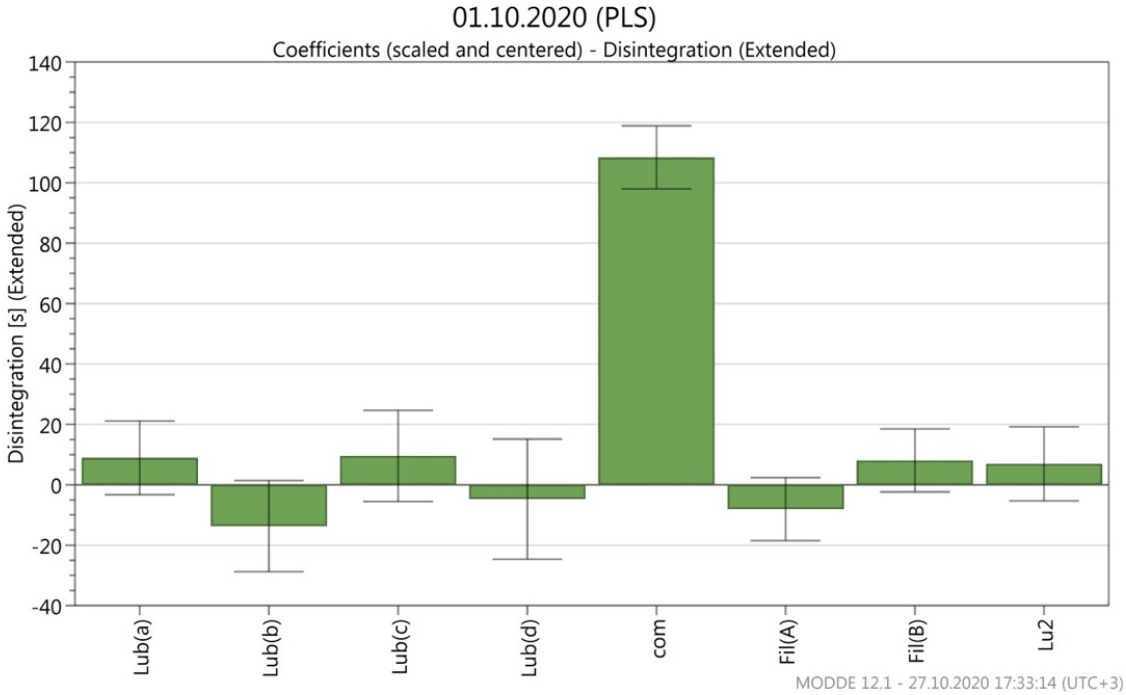


Figure 4.18. Overview plots for model evaluation of Disintegration and the values of the regression coefficients of the model equations.

4.6.2.1.3 Friability Modde Analysis

Filler type models as well as compaction force show notable effect on friability. For other responses uncertainty level does extand across y=0. Overall, using Fil (B) (MicroceLac® 100) in formulation causes an increasing on friability and when using Fil (A) (Cellactose® 80) show decreasing effect on friability as seen in Figure 4.19.

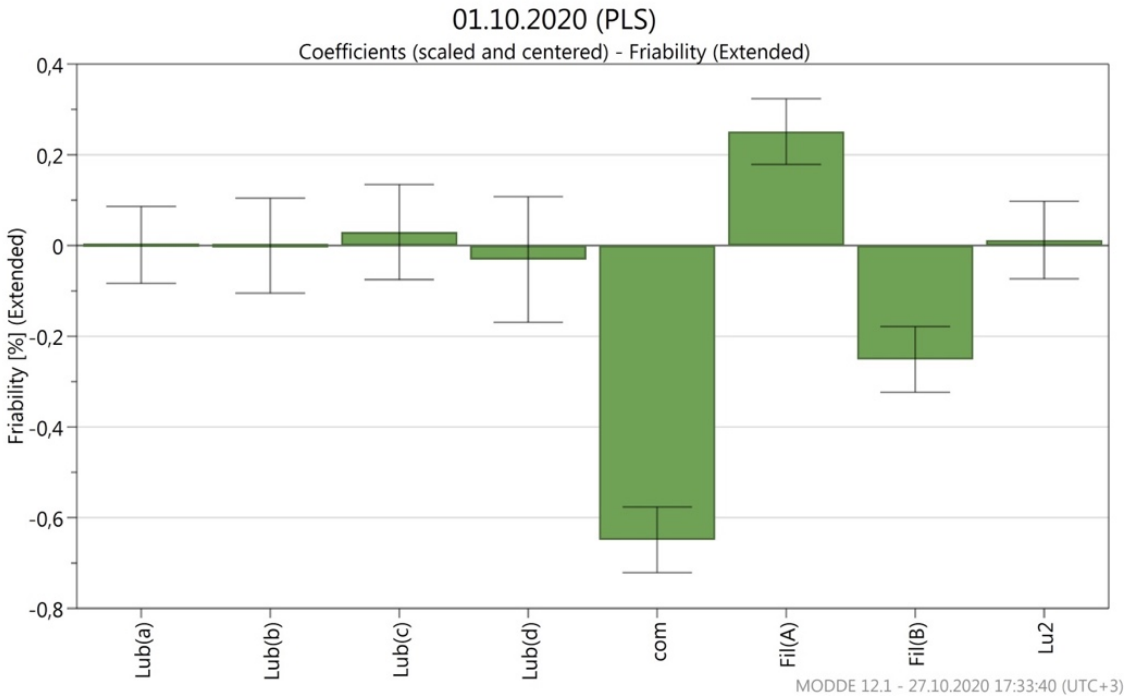


Figure 4.19 Overview plots for model evaluation of Friability and the values of the regression coefficients of the model equations.

4.6.2.1.4 Ejection Force Modde Analysis

As seen in figure 4.20, filler type does not have a significant effect on ejection force. Lubricant type and amount indicate the magnitude of the effect on ejection force only. Lubricants are used in tablet formulations to minimize wear of punches and dies thus preserving tooling by reducing die-wall friction and ejection force (Wang et al., 2013). Type of lubricant is critical in tablet formulations due to its substantial effect on ejection force. As seen in the histogram, Figure 4.16, using Lub B (Stearic acid) or Lub D (No lubricant) has an enhancing effect on ejection force while using Lub A (Magnesium Stearate) or Lub C (Sodium Stearyl Fumurate) has a reducing effect. Compaction force is seen to cause an increase in ejection force.

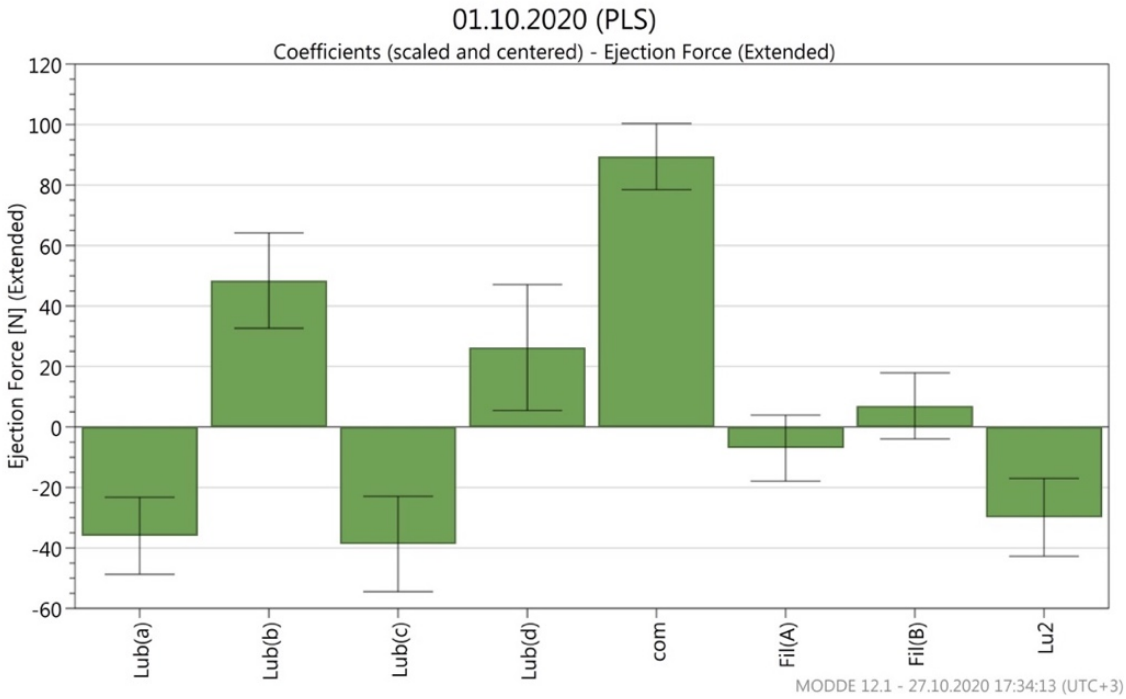


Figure 4.20 Overview plots for model evaluation of Ejection Force and the values of the regression coefficients of the model equations.

4.6.3 Design Space Development and Optimisation

The design space was generated in this study using Modde (Modde 12.1, Sweden) and PLS (Partial Least Square) models developed from the formulation and process factors to model responses are the basis for the establishment of DS.

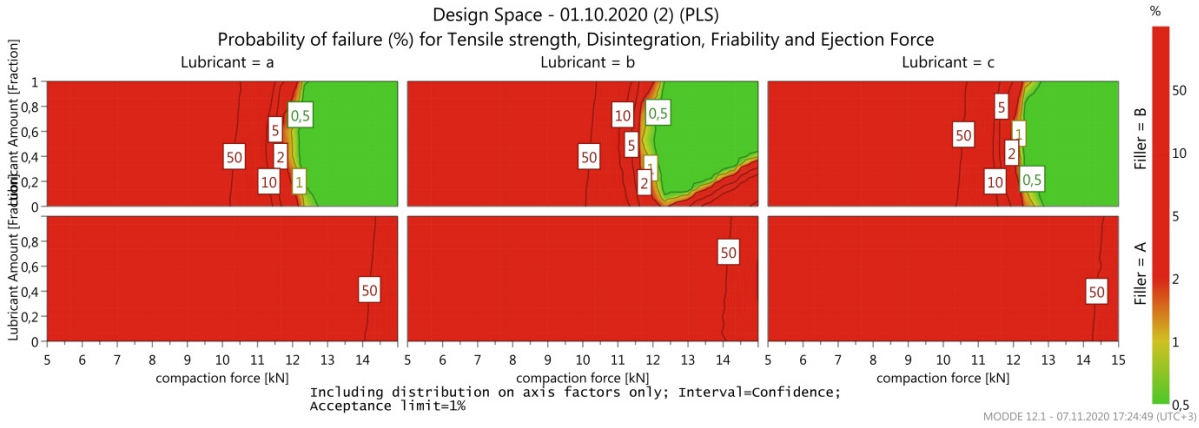


Figure 4.21 4D design space pilot for all factors. Lubricant type; a:Magnesium stearate, b: Stearic acid, c:Sodium stearyl fumurate, d:no lubricant and Filler type; A: Cellactose® 80, B:MicroceLac® 100.

In Figure 4.21, DS is presented as a function of the lubricant amount and compression pressure that fulfilled the QTPP. The green areas are part of the design space, with a less than 1 percent risk of failure. From yellow to red, the regions with a higher probability of failure are denoted.
With regard to the qualitative variables (filler type), only Type A; MicroceLac ® 100 satisfied the QTPP.

In Table 4.4, response goals for the optimizer are provided. Statistical data analysis predicted the optimum formulation to contain MicroceLac® 100 as a filler and Magnesium Stearate as lubricant at 0.22%. The optimized compaction force was predicted as 15kN. Alternative set points were suggested by the optimizer, where the initial set point was chosen based on the percent failure probability and Log(D) (normalized distance to the target). From the selected initial set point, the design space for optimal factors was generated using the robust set point function given in Table 1.

The Monte-Carlo simulation runs the robust set point function with the following settings: a resolution of 16, an iteration of 50,000, and a 1 percent failure limit probability.
Resolution describes the number of sections divided by each factor set. How many simulations are performed in each section is defined by iteration.

The probability of having predictions outside the response requirements is measured as the probability of failure expressed in percent or DPMO (defects per million opportunities) (Nie et al., 2018; Taipale-Kovalainen et al., 2018).

Table 4.4 The optimizer set points with factor settings and predicted response values, and the robust set point of factors and corresponding responses.

	Response objectives	**Optimizer initial set point**	**Robust set point**	log(D)	Cpk
Response					
Tensile strength	Maximize	2,40624	2,17888	-10	5,54796
Disintegration	Minimize	239,251	210,257	-10	16,1004
Friability	Minimize	0,392778	0,563317	-0,811706	1,98881
Ejection Force	Minimize	365,447	343,524	-0,335448	2,94389
Factor					
Lubricant		a (MgStearate)	a (MgStearate)		
compaction force		14,9992	13,6667		
Filler		B (Mi)	B (Mi)		
Lubricant Amount		0,21789	0,2		

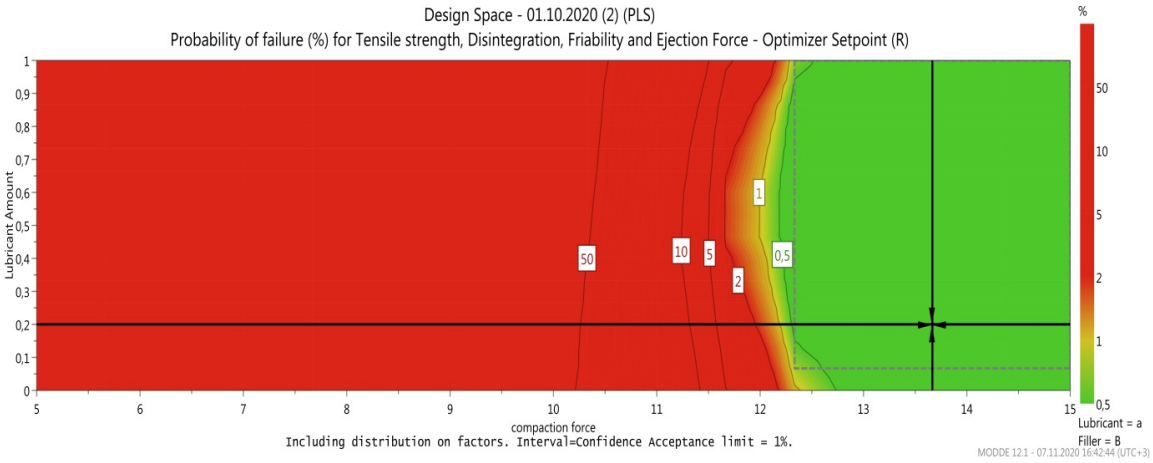


Figure 4.22 Design space plot of optimal parameters for Tensile strength, disintegration, friability and ejection force.

In Figure 4.22, the color scale represents the probability that the Quality Target Product Profile will not be satisfied. The gray-dashed box shows the current limits of the normal operating range used in the production process of tablets. As a cross with arrows, this optimum robust setpoint is shown. The alternative representation of the DS in the cas

e of multi-dimensional DS is to describe a hypercube that defines the edges of the DS. The lowest and highest values for the set point, the hypercube edges of DS with the normal operating range are represented in Table 4.5.

Table 4.5 The hypercube edges of the Design Space

Factors	**Robust setpoint**	**Low**	**High**	**SD**	**Hypercube low Edge (NOP*)**	**Hypercube high Edge (NOP*)**
Compation Force	13,6667	11,2511	13,6667	1,23246	12,3333	15
Lubricant Amount	0,2	0	0,2	0,25095	0,6666	1
Lubricant Type	Magnesium Stearate					
Filler Type	Mi					

*Normal Operation Range

4.6.4 Design Space Verification

Design space verification were done by compacting and applying Compact characterization the tests on robust set point, lowest and highest values of set point and edge points of normal operating range. Optimized formulations were pressed as seen in table 4.6 below. Final product control tests were carried out, Friability, Tensile strength, Disintegration and Ejection force were measured. All results were found within acceptable limits determined by QTPP.

Table 4.6 Formulations to verify design space.

Code	**Ibuprofen DC 85W (mg)**	**MicroceLac® 100 (mg)**	**Magnesium Stearate (mg/%)**	**Compaction Force (kN)**
OF1	200	200	(0.2)	13.67
OF2	200	200	0 (0)	11.25
OF3	200	200	(0.69)	16.08
OF4	200	200	(0.25)	12.33
OF5	200	200	(0.67)	15

4.6.4.1 Assay test

The results of the assay of chemical content using UV analysis to determine the amount of ibuprofen present in each formulation is seen in Table x. The USP stipulates that tablets should contain not less than 90% and not more than 110%. All formulations passed assay test, as seen in Table 4.7.

Table 4.7 Drug concentration (%) for assay test on optimized formulations.

Formulation	Drug Concentration (%)
OF1	98.39
OF2	99.62
OF3	102.93
OF4	99.04
OF5	103.21

4.6.4.2 Dissolution Study for Optimized formulations

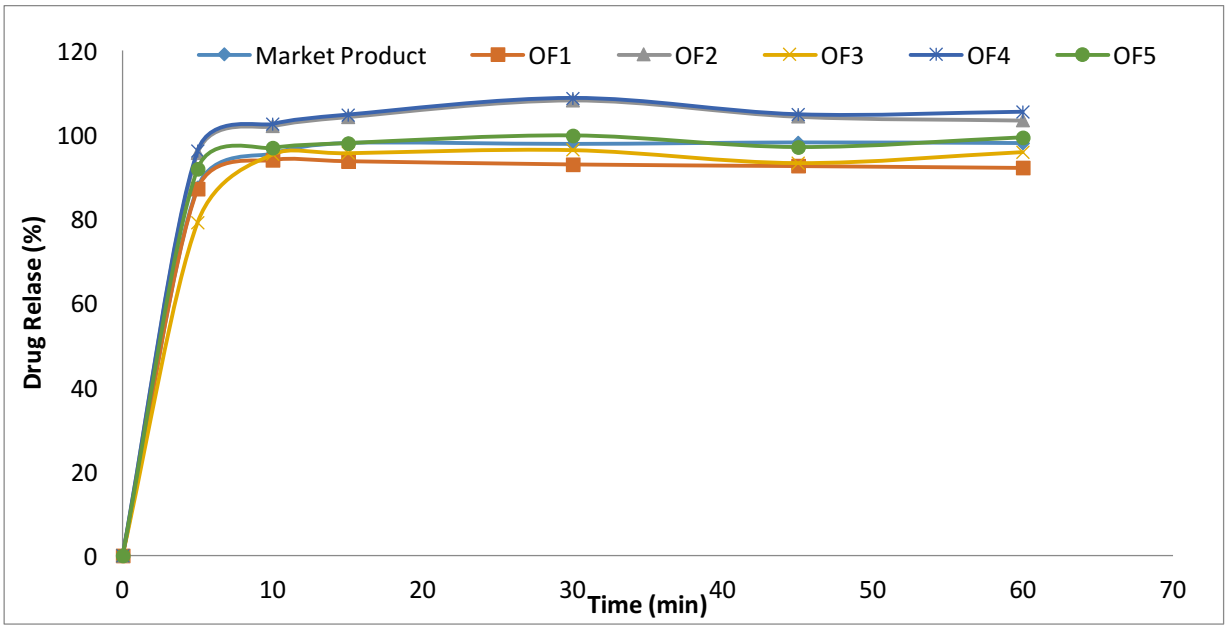


Figure 4.23 Dissolution profile for formulations at hypercube edges of the design space and market product.

Dissolution tests were carried out on the hypercube edges of the design space as seen in Figure 4.23. Formulations OF2 and OF4 showed the highest drug release. However, all formulations passed minimum USP dissolution requirements (≥ 80% in 60 minutes). Therefore, are within acceptable limits determined by QTPP (Gohel et al. 2007).

F2 values were calculated to compare optimized formulations with the market product (Fourrts). As seen in Table 4.8, OF1, OF3 and OF5 all showed F2 values of >50 therefore are considered similar. However, OF5 is considered the closest, with F2 value of 73.8. OF2 and OF4 both have the lowest similarity to market product however have an increased release profile in comparison, as seen in Figure 4.23.

Table 4.8 F2 values for optimized formulations in comparison to market product.

Formulations	F2 VALUE
OF1/MP	52.21
OF2/MP	37.81
OF3/MP	55.44
OF4/MP	35.69
OF5/MP	73.80

4.6.4.3 Assay and Dissolution Study Validation

Precision was determined by analyzing the drug at particular concentration for five times on the same day. Inter day precision was determined similarly, analyzing the samples daily, for three consecutive days.

To ensure accuracy of the method, recovery studies were performed by standard addition method at 80%, 100% and 120% levels of drug concentration, to the pre-analyzed samples and percent recovery values were calculated. Recovery experiment indicated the absence of interferences from the commonly encountered pharmaceutical additives and excipients.

The linearity studies were performed by plotting different concentration of standard solution against their respective absorbance's. Correlation co-efficient value were found to be 0.999.

The proposed method was found to be simple, accurate, precise, simple, sensitive, robust and cost effective. The results of the validation tests were found to be satisfactory and therefore this method can be applied successfully for the estimation of Ibuprofen in tablet dosage form.

CHAPTER 5
CONCLUSION

The objective of this research was to determine robust and stable manufacturing process settings by developing a design space based on the investigation of attributes dependent on lubrication, filler, and compression pressure that would impact the direct compression tableting process.

Through this study, the desired product quality profile (QTPP) and critical product quality characteristics (CQA) were defined by applying the concept of QbD. As a conclusion of the DS, the QTPP satisfied relatively large ranges of factor settings with regard to the quantitative factors. Thus, it can be said that the product that satisfies the QTPP can easily find robust factor settings.

Powder morphology and excipient characteristics were seen to strongly influence plastic deformability and tabletability of excipients used in pharmaceutical formulations. Structural differences between both fillers lead to visible differences in compaction behaviour and deformation. The results revealed MicroceLac® 100 as the superior filler as well as Magnesium Stearate at 0.2% as the optimum lubricant. At 13.7kN compaction force.

This thesis proved that QbD as a tool can be used to better understand the effects of lubricants, fillers and of the compression force on compressibility characteristics of Ibuprofen DC 85W tablets. It enriches the understanding of the effect of excipients in formulation and assists in improved formulation design.

Future study on the effect of mixing time as well as speed on lubricants may give insight and understanding of excipient behaviour. Use of compaction simulator to smooth scale-up transition can be studied, which assists formulators on an industrial scale.

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Investigation of Lubricant Effect on Ibuprofen DC and Co-Processed Lactose-Based Excipients; Pre-formulation Studies Using a Simulator

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Abstract

The aim of this study was to evaluate compaction and deformation data produced by a single punch compaction simulator to characterize the deformation behaviour and compaction properties of two co-processed lactose-based fillers, as well as to determine the efficiency of MgSt and optimize the required amount in the formulations. Using a compaction simulator in the pre-formulation step at different pressures (50MPa- 150MPa) is a valuable way of understanding pharmaceutical excipients' behaviour.

Magnesium stearate (MgSt) was used at concentrations ranging from 0.5 and 1% in formulations containing DC grade Ibuprofen DC 85 W, which was selected as the model drug. MicroceLac® 100 (75% alpha-lactose monohydrate and 25% microcrystalline cellulose) and Cellactose® 80 (75% alpha-lactose monohydrate and 25% powdered cellulose) were selected as co-processed fillers in the formulations.

Powder characterization was performed with SEM and true density test. Tensile strength was calculated and the mean yield pressure (Py) obtained by Heckel plots was used to describe the deformation mechanisms of the two fillers. Ejection forces were calculated to understand lubricant sensitivity.

Formulations containing MicroceLac®100 showed better tensile strength (2.67MPa) compared with Cellactose®80 (2.00MPa) both with and without the addition of lubricant. Differences in formulation composition led to differences in tablet strength as well as deformation behaviour. Ibuprofen formulation (Ib/M1-2) containing MicroceLac® 100 was found to be the optimum combination.

The relationship between MgSt concentration and ejection force was studied and the amount of lubricant was predicted and optimized with minimum effect on tablet hardness.

Key Words

Compaction Simulator, Co-processed lactose, Direct compression, Ibuprofen DC 85 W, Magnesium Stearate.

INTRODUCTION

A compaction simulator is defined as a device capable of mimicking the exact cycle of a tablet press and recording the parameters in real time. It is used to study powder compaction behaviour and fundamental material characterization using different compression parameters such as compression force and punch displacement [1]. Compaction simulators have the ability to reproduce upper and lower punch displacement profiles in order to obtain information about powder compressibility. They are multifunctional machines that are capable of assisting in all phases of drug development and production in the pharmaceutical industry [1-4]. During the development phase of tablet formulation, lubricant efficiency is determined using data obtained from the compaction simulator.

Lactose is commonly used as a filler in pharmaceutical tablets. It is available in several commercial grades that are produced using different manufacturing processes. These grades differ in composition, particulate and powder properties. Cellactose® 80 and MicroceLac® 100 are spray dried lactose based co-processed excipients used in direct compression. Cellactose® 80 is composed of 75% α-lactose monohydrate and 25% powder cellulose, and MicroceLac® 100 is composed of 25% microcrystalline cellulose (MCC) and 75% α-lactose monohydrate. Co-processing is defined as the combination of two or more established excipients by a pharmaceutical process. The products formed are physically modified such that they do not lose their chemical structure and stability. This means that excipients maintain their independent chemical properties while synergistically increasing their functional performance. Usually, a co-processed material exhibits superior properties than the physical mixture of individual components [5]. Ideally, a combination of a plastic and a brittle deforming material is desired for co-processing. Lactose is known to have brittle deforming behaviour, where cellulose derivatives are seen to have increased plastic deformation [6]. This combination prevents the storage of excess elastic energy during compression, which is associated with the compacts' tendency for capping and lamination [7].

Lubricants are a minor but essential formulation component in the tabletting process. Technically, they minimize wear of punches and dies, thus preserving tooling by reducing die-wall friction, in addition to preventing fill material from sticking to the punches and dies [2,8]. Their physico-chemical structure as well as the range in formulation (usually 0.25%–5.0%), significantly affects the lubrication efficiency [9].

As a lubricant in production, MgSt has a tendency to form a coating around individual particles during the mixing process, while the film formation remains largely intact throughout the compression process and may have a negative effect on tablet strength [2,8].

An indicator of the need for lubricity in the tablet can be determined by measuring the

ejection force, which is valuable data for understanding whether a material will stick to the die wall [8,10].

Ibuprofen (Ibuprofen DC 85 W), a non-steroidal anti-inflammatory compound, was selected as a directly compressible (DC grade) model drug in order to understand material behaviour with the compaction simulator [11]. Formulation behaviour was compared using compaction pressure and tablet strength data. The ejection force data were evaluated to understand the importance of lubrication for directly compressible materials. MicroceLac® 100 and Cellactose® 80 were selected as co-processed fillers in the formulations.

This study provides an insight into the composition differences between both fillers, focusing on the cellulose component, where MicroceLac® 100 contains microcrystalline cellulose and Cellactose® 80 contains cellulose fibres. The main objective was to evaluate the data produced by the compaction simulator to characterize the deformation behaviour and compaction properties of two co-processed lactose-based fillers, as well as to determine the efficiency of MgSt and optimize the required amount in the formulations.

MATERIALS AND METHOD

Materials

Ibuprofen DC 85 W, Cellactose® 80 (75% alpha-lactose monohydrate and 25% powdered cellulose), MicroceLac® 100 (75% alpha-lactose monohydrate and 25% microcrystalline cellulose) were kindly donated by BASF (Ludwigshafen, Germany) and Meggle (Wasserburg, Germany), respectively, while Magnesium Stearate MF3V1 was purchased from Peter Greven (Germany).

Powder characterization

True density

True density corresponds to the exact volume occupied by the material, without porosity. Powders were measured using a Quantachrome Ultrapyc 1200e Helium pycnometer (Yildiz Technical University, Istanbul, Turkey), using helium to determine the volume of the sample, by measuring the pressure change of helium in a calibrated volume. After the sample weight was specified, apparent particle density was derived automatically [12]. Values were expressed as the mean of three measurements.

Morphological studies

Particle morphology was assessed by Zeiss EVO/LS10 (Yildiz Technical University, Istanbul, Turkey) scanning electron microscopy (SEM). A single layer of powder was

attached to metal stubs using double-adhesive carbon tape. Subsequently, the powders were sputtered with gold under argon. Images were taken at a magnification of 250x at an accelerating voltage of 10.00kV.

Formulation Design

In order to easily optimize the formulation and evaluate the influence of each excipient on tablet properties, different formulations were designed. These were composed of four variables: Ibuprofen DC 85 W, Cellactose® 80, MicroceLac® 100, and MgSt with varying concentrations, as seen in Table 1.

Each formulation was prepared by mixing all excipients (except the lubricant) manually for 15 minutes. Subsequently, magnesium stearate was added (as the lubricant) and mixed for an additional 5 minutes consistently.

Table 1: Tablet formulation compositions with varying excipient concentrations.

Formulation Code	Ibuprofen DC 85 W (mg)	Cellactose® 80 (mg)	MicroceLac® 100 (mg)	Magnesium Stearate mg/ (%)	Tablet weight (mg)
Ib-O	400	-	-	-	400
Ib-2	400	-	-	2 (0.5)	402
Ib-4	400	-	-	4 (1.0)	404
Ce-O	-	400	-	-	400
Ce-2	-	400	-	2 (0.5)	402
Ce-4	-	400	-	4 (1.0)	404
Mi-O	-	-	400	-	400
Mi-2	-	-	400	2 (0.5)	402
Mi-4	-	-	400	4 (1.0)	404
Ib/Ce-0	200	200	-	-	400
Ib/Ce-2	200	200	-	2 (0.5)	402
Ib/Ce-4	200	200	-	4 (1.0)	404
Ib/Mi-0	200	-	200	-	400
Ib/Mi-2	200	-	200	2 (0.5)	402
Ib/Mi-4	200	-	200	4 (1.0)	404

Formation of Compacts

A compaction simulator with cams (Stylcam 200R, Medelpharm, France) and its data acquisition software (Analis, 2.01 version, Medelpharm) were used in this work. This simulator is a single station press with two punch holders. Each punch holder moves with the help of a rotating cam. By design, the upper punch and the lower punch move in a symmetric way during the pre-compression and compression phases. According to the simulated rotary press, the rotation of the cams is accelerated or slowed down [3].

Tablets were produced at different compaction forces (5kN and 15kN) and then converted to pressure (MPa), which is calculated as the force exerted per unit area. The forces were measured with strain gauges located on the upper and lower punch holders, with an accuracy of 10N. The accuracy of punch displacement, measured with potentiometric displacement transducers on the punch holders, was 0.01mm. The displacement and the force sampling rates were 5000Hz. Standard Euro B tools with 11.28 mm round, flat-faced punches were fitted on the simulator. A Fette 102i rotary press was simulated in this study [4]. Tablets were pressed at a consistent compaction speed of 10tbs/min.

The machine deformation (including punch deformation) was taken into consideration during the compression cycles.

Ejection force has been commonly used to evaluate the friction during tableting. The compaction simulator produces ejection force data in order to evaluate the efficiency of the lubricant [10].

Compact characterization

Determination of tablet tensile strength

Crushing strength (Breaking Force) of a compact was determined by pressing it diametrically (Erweka TBH 225 Series).

Tensile strength is calculated since it is independent of tablet dimensions and is a measure of the compact's strength.

Radial tensile strength of tablets (σ) was obtained from Eqn. (1).

$$\sigma = \frac{2F}{\pi . D . h} \qquad (1)$$

where F, D, and h are the breaking force, tablet diameter, and thickness, respectively [2].

Results were shown statistically using mean values ± standard deviation (SD) with n=3 tablets.

Heckel Analysis

Powder compression analysis was conducted using the Heckel equation produced by the Analis software of the compaction simulator. The Heckel equation used measured true density values was to calculate in-die yield pressure (Py) values in order to characterize the deformation behaviour of materials.

The deformability of the fillers was determined by recording the upper punch pressure and the height of the tablets every millisecond during the compression and decompression cycles (in-die measurements). The yield pressure of the materials was calculated from the reciprocal of the slope of the linear part of the Heckel plot. The yield pressure calculated by this method has been defined as an apparent yield pressure and is considered to reflect the total deformation of the material, i.e., including both plastic and elastic deformation [13].

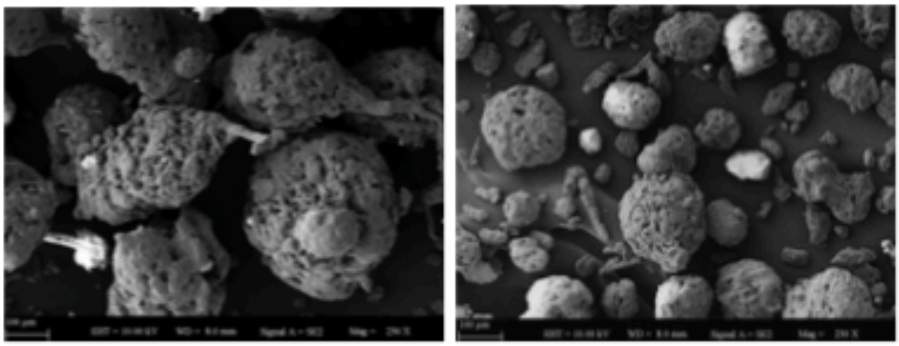
Statistical Analysis

The obtained data are presented as the mean of three experiments ± standard deviation (SD). All of the data were assessed with One-way ANOVA, followed by the Bonferroni multiple comparison test, using GraphPad Prism Software version 6.05VR (La Jolla, USA). P value < 0.05 was considered as the level of statistical significance.

RESULTS AND DISCUSSION

Powder characterization

The scanning electron microscope (SEM) images (Figure 1) showed a difference between the morphological structure of both co-processed fillers. Cellactose® 80 (Figure 1.a.) is composed of long powdered cellulose fibres that are not integrated into the particles and therefore have an irregular shape, as can be seen in the SEM images. MicroceLac® 100 (Figure 1.b.) has more entrapped, shorter fibres of microcrystalline cellulose that incorporate a more spherical form [14,15]. Cellactose® 80 is seen to have a larger particle size as well as a more uneven surface. MicroceLac® 100 is known to have better flowability than Cellactose® 80, which can be explained by its more spherical nature [14]. Differences in the morphological properties, particle size, arrangement and shape of powdered cellulose and MCC lead to differences in the compaction behaviour of the fillers.



a *b*

Figure 1: Scanning Electron Microscopy (SEM) images of the excipients used in this study (250x):(a) Cellactose® 80, (b) MicroceLac® 100.

Compact characterization

Tensile strength

Tablets which were pressed with 50MPa and 150MPa pressure by compaction simulator were evaluated. Figure 2 shows the tensile strength results for formulations containing Ibuprofen DC 85 W with different concentrations of magnesium stearate as the lubricant (0%, 0.5%, 1%) without inclusion of filler [16].

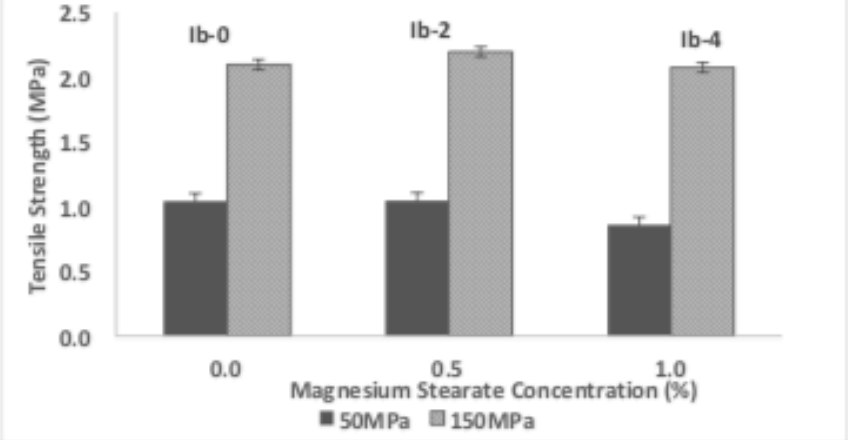


Figure 2: Tensile strength results for formulations without filler (Ib-O, Ib-2, Ib-4), compressed at 50MPa and 150MPa pressure. Data are represented as mean ± SD (n=3).

The results show that the tablets produced have significance ($p<0.05$) with increased tensile strength at higher compaction pressures [11]. This is due to the increase in inter-particulate interaction and subsequent improvement in tablet strength [17]. At 150MPa, tensile strength values ranged from 2.07MPa for Ib-4 and 2.19MPa for Ib-2, indicating that Ibuprofen, without the addition of filler, is not significantly affected by changes in lubricant concentration.

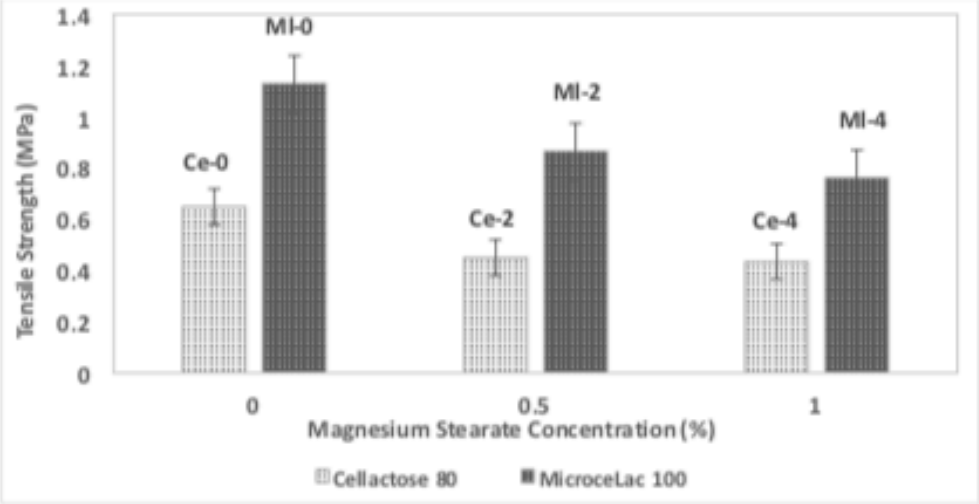


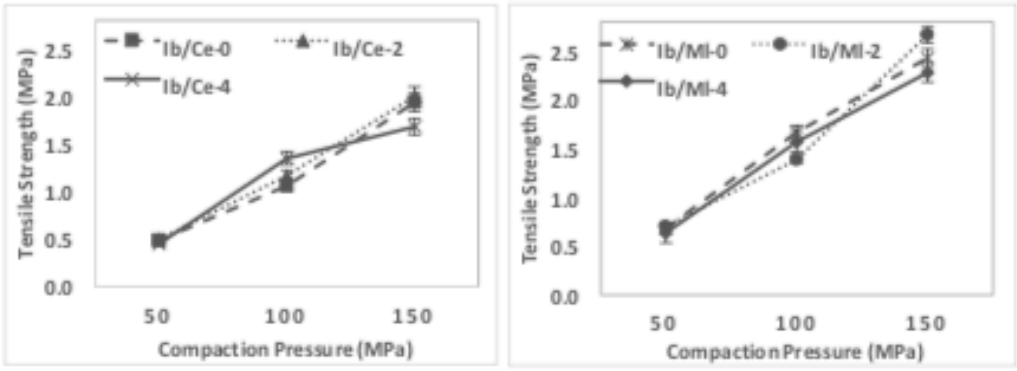
Figure 3: Tensile strength values for placebo tablets compressed at 50MPa containing Cellactose® 80 and MicroceLac® 100 at different magnesium stearate concentrations. Data are represented as mean ± SD (n=3)

As seen in Figure 3, Ce-0, Ce-2, Ce-4 are all formulations containing Cellactose® 80, whereas Ml-0, Ml-2, Ml-4 contain MicroceLac® 100 with different concentrations of lubricant (0%, 0.5%, 1%). MicroceLac® 100 containing formulations show favourable tensile strength values (0.76-1.13MPa) compared to formulations containing Cellactose® 80 (0.65-0.43MPa) ($p<0.05$). Although not significant, it is also observed that as the concentration of MgSt increases, the tensile strength decreases for MicroceLac® 100.

The tensile strength results (Figure 2 and Figure 3) are concurrent with the findings of previous studies. They show that an increase in lubrication concentration causes a negative

effect on tablet strength. This is dependent on the attractive forces and contact between particles over the entire contacting area. Eventual tablet strength is affected by the fine lubricant particles interfering with the interactive bonding forces between particles. The negative effect of MgSt has more impact on plastically deforming materials. [7,9,18].

Figure 4 shows combination formulations containing Cellactose® 80 (Ib/Ce-0, Ib/Ce-2, Ib/Ce4) and MicroceLac® 100 (Ib/Ml-O, Ib/Ml-2, Ib/Ml-4). In agreement with the results shown above, it is observed that MicroceLac® 100 containing formulations have a higher overall tensile strength in comparison with Cellactose® 80. Significant differences are seen at higher compaction pressure (150MPa). A similar study conducted by Muzíková and Zvolánková [18] showed concurrent results that the strength of the compacts from pure Cellactose® 80 was lower than that of those from MicroceLac® 100 both with and without the addition of lubricant. The results confirm differences due to composition and morphology, which can be seen in the SEM images (Figure 1). Smooth particles tend to have a high surface to mass ratio, which makes them more cohesive. Coarse particles are more influenced by gravity forces, which make them less cohesive, leading to lower tensile strength [19].

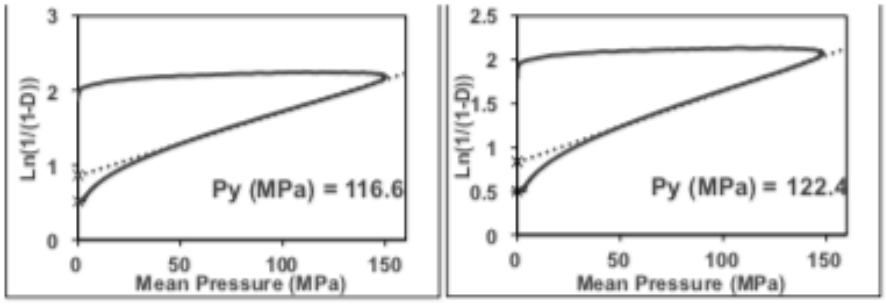


a *b*

Figure 4: Tensile strength values for formulations containing Ibuprofen DC 85 W, Cellactose® 80 / MicroceLac® 100 and different MgSt concentrations at different pressures. Data are represented as mean ± SD (n=3)

Heckel Analysis

Important material properties, particularly Yield pressure (Py), is calculated from the linear slopes k in order to characterize the deformation behaviour of materials. As seen in Figure 5, pure unlubricated Cellactose® 80 (Py-116.6MPa) containing powdered cellulose component is more plastically deforming in comparison to pure unlubricated MicroceLac® 100 (Py-122.4MPa) containing microcrystalline cellulose component, as seen by the lower Py value (Py-116.6). Differences in powder composition lead to differences in deformation mechanisms as well as tablet strength [13, 20].



(a) Cellactose® 80 (b) MicroceLac® 100

Figure 5: Heckel plots for two fillers (a) and (b) produced by compaction simulator at 150MPa pressure.

Ejection force

Figure 6 shows the measured ejection force values produced by the compaction simulator. A high ejection force is indicative of high friction at the tablet–die wall interface. Excessive friction can damage the tablet and reduce tooling life by wearing. Pure, unlubricated Cellactose® 80 shows an overall decreased ejection force compared to unlubricated MicroceLac® 100. A previous study showed that ejection tends to decrease more rapidly with increasing compaction pressure for materials with lower yield pressure [10]. This is concurrent with the results of the present study, which show that Cellactose® 80 (Py-116.6MPa) has a reduced ejection force in comparison to MicroceLac® 100 (Py-122.4MPa).

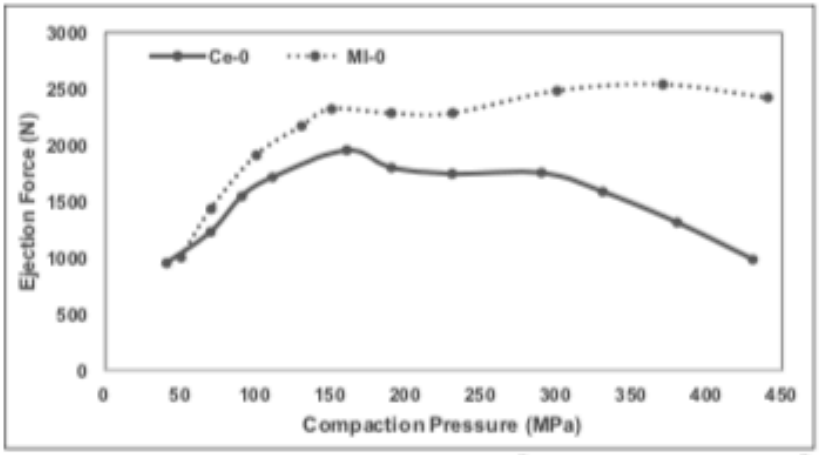


Figure 6: Comparison of ejection force data of Cellactose® 80 (Ce-O) and MicroceLac® 100 (MI-O) Data are represented as mean ± SD (n=3)

A lubricant concentration effect on ejection force for all combination formulations is seen in Figure 7. Formulations containing pure Cellactose® 80 show decreased ejection force compared to pure MicroceLac® 100 (as seen in Figure 6); however, the differences observed are not as prominent when in combination with Ibuprofen DC 85 W.

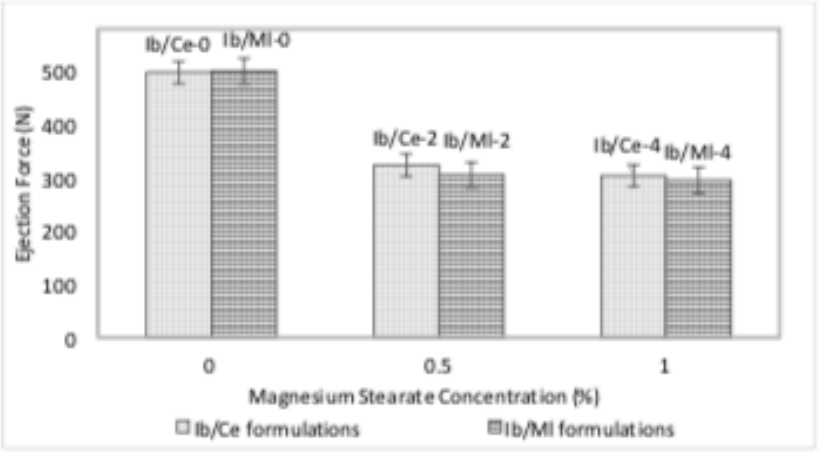


Figure 7: Comparison of ejection forces for all formulations compressed at minimum pressure (50MPa). Data are represented as mean ± SD (n=3)

The different behaviour of the fillers is due to the variance in the composition and particle characteristics as seen in the SEM results (Figure 1a and b). An increase in MgSt concentration causes a decrease in ejection force for both Cellactose® 80 (498N at 0% MgSt Conc. to 304N at 1% MgSt Conc.) and MicroceLac® 100 (501N at 0% MgSt Conc. to 296N at 1% MgSt Conc.), which is to be expected as it was reported in previous studies [2,10]. Reduced ejection force reduces wear on punches and makes the tableting process more efficient. Ejection force values indicate that 0.5% MgSt is efficient in this formulation, as an increase in MgSt concentration to 1% does not improve the ejection force values significantly.

As a result, the characteristics of the fillers may serve as a useful tool for evaluating their effectiveness and formulation efforts. An attempt was made to observe the differences in the behaviour of two fillers in combination with the model drug Ibuprofen DC. The obtained data supports that the selection of fillers affects the compressibility of the formulations. The addition of filler improves the efficiency of compression by reducing the ejection force and increasing the robustness of formulation.

CONCLUSION

This study proves that powder morphology and excipient characteristics strongly influence plastic deformability and tabletability of excipients used in pharmaceutical formulations. Structural differences between both fillers led to visible differences in compaction behaviour and deformation.

The amount of MgSt required was predicted and optimized with minimum effect on tablet hardness. The use of measured tensile strength and ejection force data assisted in selecting an optimum amount.

It can be concluded that Ib/Ml-2 was determined as the optimum formulation, containing MicroceLac® 100 with 0.5% MgSt pressed at 150MPa pressure due to the maximal tensile strength and acceptable ejection force in relation to all other formulations.

It was proven that the addition of more than 0.5% MgSt in the formulation has no significant positive effect.

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Conflict of interest

The authors declare that they have no conflict of interest.

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SPSS	Good

***Evaluate as very good, good, moderate, poor.

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