TURKISH REPUBLIC OF NORTH CYPRUS
NEAR EAST UNIVERSITY
HEALTH SCIENCES INSTITUTE

QbD APPROACH FORMULATION DESIGN FOR POORLY SOLUBLE DRUG NIMESULID AND EVALUATIONS

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MASTER THESIS

PHARMACEUTICAL TECHNOLOGY DEPARTMENT

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2019-NICOSIA

STATEMENT (DECLARATION)

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.

Hala Khamis

Signature

ACKNOWLEDGEMENTS

Thanks to Allah Almighty for giving me wisdom, strength and in helping me surpass all the obstacles faced in order to accomplish this study. Alhamdulillah one of my biggest dreams in obtaining a postgraduate degree in my future field was accomplished and that I am one step closer in achieving more of my goals.

With boundless love and appriciation, I dedicate my work to my mother, a lovely soul how taught me to trust in Allah and work hard and that with her support my dream was accomplished. Also, I dedicate this work to my father who I wouldn't be here in the first place without him.

I would like to extend my deepest sincerest gratitude to my advisor **Assoc. Prof. Dr. Yıldız ÖZALP** for her guidance, patience, immense knowledge and support throughout my journey in which it was a privilege and honor to have shared an amazing experience from her.

Also, my heartiest gratitude for my co-advisor **Assoc. Prof. Dr. N. Buket AKSU,** for her support and cooperation throughout this journey along with Altınbaş University.

I also would like to thank the assistance group whom supported me in my work spiritually and practically. Many thanks to my friend and assistant **Nailla Jiwa** who played a major role in my work. Also, to Joseph and Mayowa for their efforts and advice.

Last but not least, special thanks to my friends **Alaa, Omar, Mussab** and **Adel,** for their support, patience, collabiration and for being such good friends throughout this journey.

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LIST OF ABBREVIATIONS

API:	Pharmaceutical Ingredient
QbD:	Quality by Design
ICH:	International Conference on Harmonization
EP:	the European pharmacopeia
FDA:	Food and Drug Administration
CMC:	Critical Micelle Concentration
NSAIDs:	non-steroidal anti-inflammatory drugs
BCS:	Biopharmaceutical Classification System
COX:	Cyclo-Oxygenase
mg:	Milligram
L:	Liter
pH:	potential hydrogen
GIT:	gastrointestinal tract
W/W:	Weight Concentration
°C:	Degrees Celsius
Kg:	Kilogram
cm:	Centimeter
g:	Gram
ml:	Milliliters
m:	Meter
µm:	Micrometer
rpm:	Revolutions per Minute
h:	Hour
θ:	Theta
mm:	Millimeter
pKa:	the acid dissociation constant

N:	Newton
dm/dt:	the rate of dissolution of the drug particles
D:	The diffusion coefficient of the drug in solution in the gastrointestinal fluids.
A:	The effective surface area of the drug particles in contact with the gastrointestinal fluids.
h:	The thickness of the diffusion layer around each drug particle
Cs:	The saturation solubility of the drug in solution in the diffusion layer.
C:	The concentration of the drug in the gastrointestinal fluids (bulk concentration).
IR:	Immediate Release
MDCK:	Madin Darby Canine Kidney
SGF:	Simulated Gastric Fluid
SIF:	Simulated Intestinal Fluid
USP:	The United States Pharmacopeia
HLB:	Hydrophilic- Lipophilic Balance
r:	radius
BET:	Brunauer-Emmett-Teller
λ:	Wavelength
DC:	Direct Compression
MCC:	Microcrystalline cellulose
CL:	Chloride
M:	Tablet Diameter
T:	Tablet Thickness
BFE:	Basic Flowability Energy
TPP:	Target Product Profile
QTPP:	Quality Target Product Profile
CPP:	Critical Process Parameters
CMA:	Critical Material Attributes

CQA:	Critical Quality Attributes
N:	Normality
FMEA:	Failure mode effects analysis
ppt:	Precipitate
x:	Magnify
MN:	Mega newton
sec:	Seconds
IR-Spectrum:	Infrared Spectroscopy Spectrum
Mpa:	Mega pascal
Py:	yield pressure
cm^3:	Cubic centimeter
R^2:	the Coefficient of Determination
Rt and Tt:	the Cumulative Percentage Dissolved
n:	Time Point
D:	The Relative Density
K:	Slope
CD:	Cyclodextrin
P:	The Pressure
A:	The Intercept of the Extrapolation of the Straight Portion of The Line
Py:	Yield Pressure
PPM:	Parts Per Million

QbD Approach Formulation Design For Poorly Soluble Drug Nimesulid And Evaluations

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SUMMARY

Aim: To understand excipients effect on formulation of low soluble active pharmaceutical ingredients (API). In order to optimize composition and quality parameters by QbD approach, Nimesulid is chosen as poorly soluble model API.

Material and Method: Analytical study of Nimesulide composing of different pH's calibration curves and pH 7.4 solubility study was conducted. Marketed products (NS, ND) quality control tests were done and evaluated. Preformulation studies was done by using Flowlac®100 and Avicel®102 as fillers, variable concentrations of Kollidon®30 as binder, Kollidon®CL and Primojel® as superdisintegrants, and magnesium stearate was as a lubricant. Tableting process was conducted using direct compression (DC) method by using compaction simulator at two applied forces 5,10 kN. The Quality Target Process Parameter (QTPP) results were used to applied the umetric Modde software program in order to obtain a design space by QbD approach.

Findings and Results: The max. solubility of Nimesulid was calculated as 0.0776 mg/ml in pH 7.4 buffer. NS was sellected as the reference product after evaluation of test results. The formulation KOK5b containing 100 mg Nimesulid passed all the physical requirements and obtained similarity (f2) with NS product, 61.4 which is acceptable. Kollidon® CL showed higher release rate than Primojel® in the formulation without binder.

QbD approach design space was obtained. QTPP data evaluation were done except friability test and optimum formulation composition was noticed again as without binder.

Keywords: Nimesulid, Quality by Design, Direct compression

Kalite Tasarımı Yaklaşımıyla Çözünürlüğü Düşük Nimesulid Etkin Maddesinin Formülasyon Tasarımı ve Değerlendirmesi

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Anabilim Dalı: Farmasötik Teknoloji

ÖZET

Amaç: Düşük çözünürlüğe sahip etken maddelerin formülasyonlarında yardımcı maddelerin etkisini anlaşılması amaçlanmıştır. Formulasyon içeriği ve kalite parametrelerini QbD yaklaşımı ile optimize etmek için Nimesulid zayıf çözünürlüğe sahip model etken madde olarak seçilmiştir.

Materyal-Metot: Nimesulid'in farklı pH'larda kalibrasyon eğrileri ve pH 7.4 çözünürlük analitik çalışması çalışması yapılmıştır. Pazar ürünlerinden (NS, ND) kalite kontrol testleri yapıldı ve değerlendirildi. Ön formülasyon çalışmaları dolgu maddesi olarak Flowlac®100 ve Avicel®102, farklı konsantrasyonlarda bağlayıcı olarak Kollidon®30, süper dağıtıcı olarak Kollidon®CL ve Primojel® ve kaydırıcı olarak magnezyum stearate kullanılarak yapılmıştır. Tablet hazırlama işlemi, iki ayrı baskı kuvvetinde (5 ve 10 kN'de) compaction simulator kullanılarak doğrudan basım (DC) yöntemi ile yapılmıştır. QTPP sonuçları, QbD yaklaşımı ile bir tasarım alanı elde etmek için umetrik Modde yazılım programını uygulamak için kullanılmıştır.

Sonuç-Tartışma: Nimesulidin maksimum çözünürlüğü, pH 7.4 tamponunda 0.0776 mg/ml olarak hesaplandı. Test sonuçlarının değerlendirilmesinden sonra referans ürün olarak NS seçildi. 100 mg Nimesulid içeren KOK5b formülasyonun tüm fiziksel testlerin gereklerini karşıladığı ve NS ürünü ile 61.4 olan kabul edilebilir bir benzerlik (f2) elde ettiği bulundu. Kollidon CL , bağlayıcı içermeyen formülasyonda, Primojel'den daha yüksek salım hızı gösterdi. QbD yaklaşımı ile tasarım alanı elde edildi. QTPP veri değerlendirmesi aşınma testi dışında yapıldığında, optimum formülasyon içeriğinin yine bağlayıcı madde içermeyen bir öneri olduğu görüldü.

Anahtar Sözcükler: Nimesulid, Kalite Tasarımı, Doğrudan Basım.

CHAPTER 1: INTRODUCTION

1.1 Nimesulide Overview

Nimesulide is considered to be one of the most commonly prescribed non-steroidal anti-inflammatory drugs (NSAIDs) that are available at the market. It is widely used in treating a variety of inflammatory and painful conditions. For instance, post-operative pain, osteoarthritis, primary dysmenorrhea, low back pain, tonsillitis and pharyngitis.

Besides having high gastrointestinal tolerability, minimum drug-related side-effects, and a high therapeutic index, it is considered to have high anti- inflammatory, antipyretic, and analgesic activities (SINGLA et al., 2000). After the drug is administered, the analgesic effect will be attained in about 15-20 minutes, which is crucially important in acute pain syndrome (Cherniavska & Soldatov, 2016).

Recently, a noticeable increase was observed in the amount of sparingly soluble drugs, which in turn provided several challenges to the industrial pharmacist while formulating such entities (Gohel & Patel, 2003). Nimesulide exhibits poor bioavailability when administered as conventional tablets due to its poor aqueous solubility and high hydrophobicity (Piel et al., 1997). Therefore, since the key determinant of oral bioavailability is the solubility of the active pharmaceutical material then the aim of this research is to provide way to enhance the solubility of Nimesulide. This is going to be done by applying a novel way called as the Quality by Design (QbD).

1.2 Quality by Design

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 (Aksu B. M., 2012).

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 is considered to be a systemic method of pharmaceutical development. It encompasses designing, developing formulations and manufacturing process to meet a set goal in the quality of the product.

As QbD is applied, the manufacturer can guarantee the product's quality through understanding and regulating elements that are subjected to change in various solutions and procedures. Over here, the drug's chemistry, production and control will be reviewed and submitted for approval, which in turn will become scientific evaluations of pharmaceutical quality (Food and Drug Administration guidelines).

The most important part of QbD is to be aware of how the process and formulation parameters would affect the product characteristics, and to optimize these parameters respectively to the final specifications required (Lawrence, 2008).
As a result, critical parameters should be recognized to be able to monitor these parameters online as they are in the production process.

Hence, QbD is a holistic concept in which the final product specifications, manufacturing process and critical parameters are incorporated in order to facilitate the final approval and the ongoing quality control of a new drug product (McKenzie et al., 2006).

1.3 Solid Dosage Forms and Formulations

Solid dosage forms 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). Nowadays, 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). 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 (Hirani et al., 2009) (Allen & Ansel, 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 quiet 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).

Conversely, 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. 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).

Tablets can be of several types depending on their intended use and method of manufacture. In the framework of intended use. 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).

As previously mentioned, one of the challenges in formulating a poorly water soluble drug as a tablet dosage form is the poor bioavailability. Therefore, in order to prevent bioavailability problems, it is quiet important to focus on the dissolution studies of the drug during the preformulation stages. As a result, due to this obstacle, the model drug chosen for this research is Nimesulide since it has solubility issues.

CHAPTER 2: THEORITICAL BACKGROUND

2.1 Nimesulide

Nimesulide is a non-steroidal anti-inflammatory drug (NSAID). It is considered to be unique due to two reasons. Primarily, it is known to have a selective action on the Cyclo-Oxygenase (COX-2) enzyme. Secondly, is that it has a unique chemical structure differing from other compounds in that its acidic by virtue of a sulphonanilide rather than a carboxylic group, meaning that it is an acidic NSAID. Moreover, Nimesulide is classified by the Biopharmaceutical Classification System (BCS) to be a class-2 compound drug in which it resembles a drug with high permeability along with low solubility (SINGLA et al., 2000)

2.1.1 Uses

It is a commonly prescribed NSAID that usually possesses anti-inflammatory, analgesic and antipyretic activity with moderate incidence of gastric side effects and a high therapeutic index. It is mainly pointed out as second line treatment for acute pain, symptomatic treatment of painful osteoarthritis and primary dysmenorrhoea.

Nimesulide is taken as a daily dose of 100 mg twice daily with maximum duration of treatment being 15 days and the shortest duration of treatment is usually recommended (SINGLA et al., 2000).

2.1.2 Mode of Action

It mainly works by inducing the selective inhibition of the Cyclo-Oxygenase(COX-2) enzyme without (COX-1) that results alternatively in reduced production of prostaglandins along with other pro-inflammatory mediators, and therefore, it exerts an anti-inflammatory action while implying an increase opportunity in the market due to gastrointestinal tolerability and reduced prevalence of renal dysfunction (SINGLA et al., 2000).

2.1.3 Physical Properties

Nimesulide (4-nitro-methanesulphonanilide), with a molecular formula of C(13)H(12)N(2)O(5)S and a molar mass of (308.31), have its structure as illustrated in (Figure 2.1) (Singh et al., 2005).

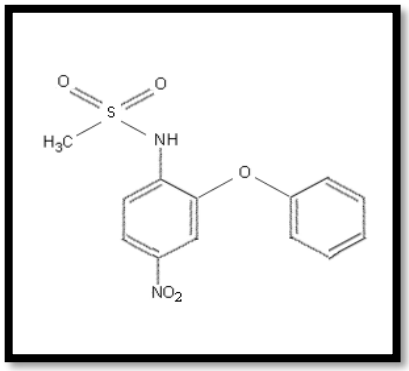

Figure 2.1: Nimesulide structure.

Nimesulide appearance exhibits a yellowish crystalline powder, which is practically odorless. It has pKa values of 5.90, 6.46, 6.50 and 6.8, which clearly indicates the acidic nature of the drug, which is the weak acidic moiety of sulphonanilide (Singh et al., 1999).

Nevertheless it has a melting point of 147-148 °C (Piel, et al., 1997) and an Octanol/Water partition coefficient of 238, corresponding to a log P value of 2.376, which in turn clearly demonstrates the lipophilic character of the drug. Nimesulide have an IR value of 3283.66 (Singh et al., 2005). Nimesulide suffered from unsatisfactory micrometric properties and flow properties (SINGLA et al., 2000).

The drug is considered to be non-hygroscopic and have a crystalline form, which makes it hard to predict it is compatibility with the excipients (Hanif, et al., 2014). Nimesulide is known to have polymorphism, in which the compound may exist in more than one different crystal structure. It consists of a mixture of two polymorphs, the stable, less soluble form I (the native form) and the metastable, more soluble form II as seen in (Figure 2.2). The morphology of form II is mainly acicular in nature, whereas form I has

rod shaped structure (Sanphui et al., 2011). It was reported that the solubility in pH 7 buffer medium of form I and form II are 16.4 and 71.0 mg/L respectively.

Moreover, equilibrium solubility study suggests that the metastable form II is considered to be 4.3 times more soluble than commercial form I. As a result of such dramatic enhancement in solubility found between the polymorphs of the drug which is known to be uncommon, therefore it would be of great solution to use the metastable form in the formulation instead of form I, but only find the right excipients to try to stabilize the polymorph during the formulation in order to prevent its transformation back to form I (Sanphui et al., 2011).

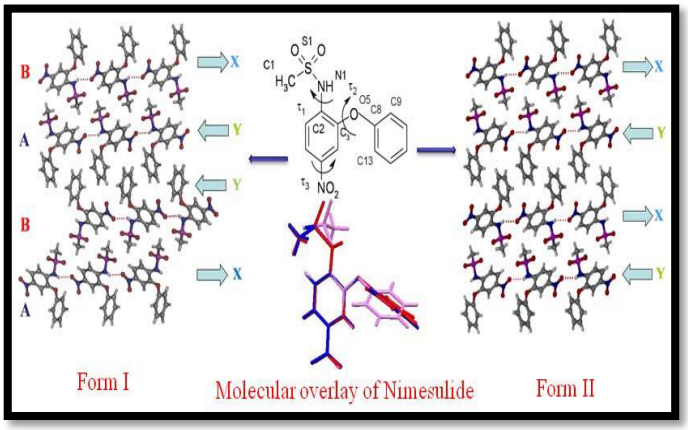

Figure 2.2: Nimesulide polymorphism.

Nimesulide exhibits a plasma half-life of 2-5 hours, meaning that it requires frequent administration (Bhattacharyya et al., 2014) and also have maximum protein bonding (Sora et al., 2007).

Most importantly, Nimesulide is considered to be moderately soluble in polar solvents such as acetone, dichloromethane, chloroform and ethyl acetate. Diminished solubility is attained in solvents expressing high polarity such as methanol. It is reported that its solubility in water is 0.01 mg/ml which indicates poor solubility. Due to the deprotonation and ionization of sulfonamide group, the solubility can be enhanced by

increasing the pH of the aqueous solution and therefore, Nimesulide is known to have pH dependent solubility (Singh et al., 2005).

Since the drug exhibits low solubility in water, it is required to administer high doses of the drug in order to maintain the plasma concentration at the therapeutic levels. This indeed results in unwanted side effects including, heartburn, diarrhea, nausea, vomiting, peptic ulcer and hepatic damages (Dashora et al., 2007).

2.1.4 Dosage Forms Available

The available dosage forms found in the market include: tablets (100 mg), granules for oral suspension (100 mg), suppositories (200 mg) and gel (3%) (Davis, 1994).

2.2 Importance of Solubility and Dissolution

One of the most critically challenging concerns witnessed in the pharmaceutical area, is the solubility behavior of the drug substances. About 40% of all new chemical entities are reported to have poor solubility and therefore poor bioavailability (Kesarwani et al., 2014). This indeed produces an enormous problem for the industry and the patient.

As it is commonly known, when the drug is administered orally, it should firstly dissolve in the gastric or the intestinal fluids in order to permeate through the membranes and enter into the systemic circulation to produce the intended pharmacological action.
As a result, if the administered drug is considered to have poor solubility then from the patient's perspective, the patient will not be able to get satisfaction since the amount of drug reaching the pharmacological site of action will not be achieved and the drug will ultimately remain undissolved in the gastrointestinal tract (GIT) and eventually excreted. Consequently, this will lead to administering the poorly water soluble drug at higher doses than the actual dose required in order to achieve the necessary drug plasma level which will result in unwanted adverse effects such as gastric irritation, peptic ulceration, etc., which will start to evolve more frequently and lead to decreased patient complains along with much expensive cost of therapy. Therefore, the oral therapeutic effectiveness of the drug is not only dependent on the bioavailability but as well as on the solubility of

the drug molecules. This is because the drug liberation process is mainly determined by the solubility factor, which in turn, affects the bioavailability.

On the other hand, from an industrial perspective, since large amount of active pharmaceutical ingredient (API) might be consumed to develop and manufacture the drug product, therefore the manufacturing cost would rise respectively. Thus, it is vital to develop solubilization technologies in order to overcome the poor solubility matter which is becoming more and more important to the pharmaceutical industry in order to open up pathways to prepare effective and marketable drugs (Bharti et al., 2015).

2.2.1 Solubility and Dissolution

The term ‘solubility’ is defined as the maximum amount of solute that can be dissolved in a given amount of solvent. Although, solubility can be expressed both quantitatively and qualitatively. Quantitatively speaking , it's considered as the concentration of solute in a saturated solution at a certain temperature whereas, qualitatively speaking, it's considered as a spontaneous interaction of two or more substances to result in a homogenous molecular dispersion. The substance to be dissolved is called as the solute and the dissolving fluid in which the solute dissolves in is called the solvent.

In terms of drug solubility, solubility can be defined as the maximum concentration of the drug dissolved in a specific amount of solvent under specific conditions of temperature and pH. This is mainly known as saturation or equilibrium solubility (Gibson, 2016) (Kumar & Singh, 2016). On the other hand, dissolution is the rate of release of a drug substance from a drug product, usually in an aqueous medium under specified conditions.

Solubility and dissolution are related terms but in fact differ from each other. It should be highlighted that dissolution is a dynamic process by which the drug dissolved is characterized by its rate (amount dissolved per time unit), whereas solubility is the amount of material dissolved per volume unit of a specific solvent (Gibson, 2016). However, both processes complete each other, since the poor solubility often leads to poor dissolution and therefore poor bioavailability and vice versa.

The main criteria used for determining the drugs equilibrium solubility is through the shake flask method. This method was applied to Nimesulide in our research and the criteria will be explained in the methods section.

According to the United States Pharmacopoeia and the British Pharmacopoeia the following classification represents the solubility regardless of the solvent used, only in terms of quantification and have defined the criteria as given in (Table 2.1).

Nimesulide is considered to be practically insoluble in water since it shows 0.01 mg/ml solubility (Shoukri et al., 2009). Moreover, it is important to illustrate that in order for dissolution to occur the solute particle size should firstly be reduced. This will in turn initiate the process of dissolution, in which it is measured as a rate. As following in (Figure 2.3) it represents the dissolution process of a tablet (Fox, 2014).

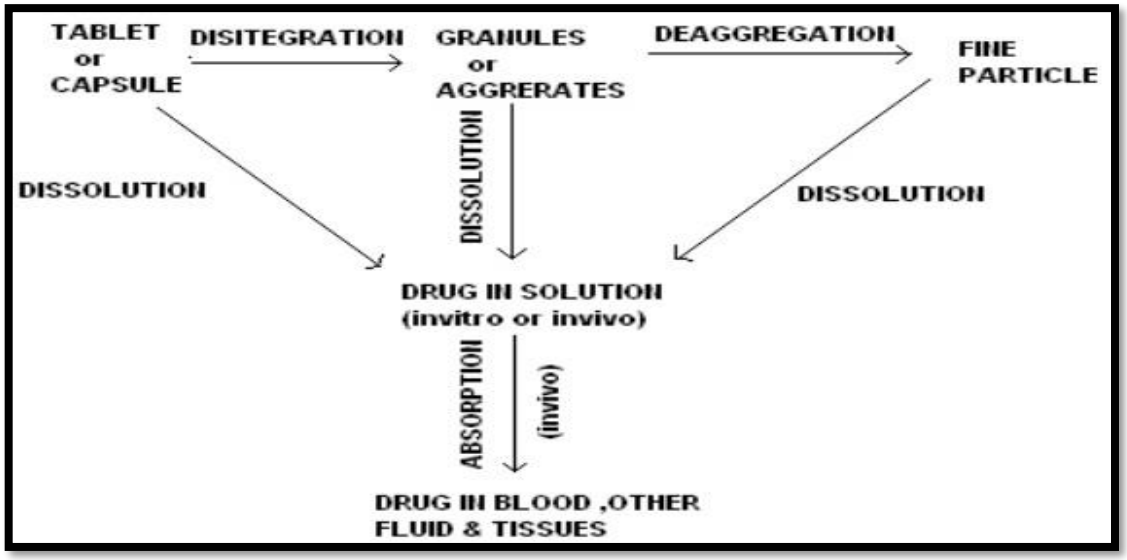

Figure 2.3: The processes involved in dissolution of solid dosage forms.

Table 2.1: Solubility Classification Criteria (United States and British Pharmacopoeia).

Descriptive term	**Parts of solvent required for one part of solute**
Very soluble	<1
Freely soluble	From 1 to 10
Soluble	From 10 to 30
Sparingly soluble	From 30 to 100
Slightly soluble	From 100 to 1000
Very slightly soluble	From 1000 to 10,000
Practically insoluble or insoluble	10,000 and over

2.2.1.1 Solubility Enhancement Techniques

There are several techniques applied now days in order to improve the solubility of the available drugs. In our research, Nimesulide was subjected through physical modifications in order to enhance its solubility. Those physical modifications were composed of micronization and solubilization by surfactant.

2.2.1.1.1 Micronization

Micronization exhibits a high energy particle size reduction technique which is mainly used for increasing the solubility of BCS class II drugs (Leleux & Williams, 2014). It is well-known to be a simple process where the coarse drug powder will be transferred into an ultrafine powder, which resembles a mean particle range of 2-5 micrometer as well as only a very little portion of the particles will lie below 1 micro meter size range (Rawat et al., 2011). As a result, the equilibrium solubility of the drug itself will not be increased but the dissolution rate will be enhanced due to the increase in the surface area to volume ratio.

Micronization results in uniform dosage form that contains uniform, narrow particle size distribution. Not to mention that micronization is not considered as an approach for drug substances having high dose number since it does not change the saturation solubility of the drug (Rawat et al., 2011).

The resulting micronized drug substance properties for instance particle size, size distribution, shape, agglomeration, surface properties behavior and powder flow are influenced by the type of micronization technique used. The following techniques are the most commonly utilized techniques for production of micronized drug particles involving micronization: Mechanical communition such as jet milling and ball milling.

1. Jet milling: It is known to be the most preferable method used in micronization. A fluid jet mill utilizes the energy of the fluid (high pressure air) to produce ultra fine grinding of pharmaceutical powders in use (Midoux et al., 1999).

2. Ball milling: A ball mill constitutes usually of a cylindrical crushing device that grinds the pharmaceutical powders by rotating them around a horizontal axis (Graeser et al., 2010).

2.2.1.1.2 Surfactants

Hydrophobic drugs can have their solubility enhanced through the use of surfactants. They are a large group of excipients that have been used in the pharmaceutical formulations as drug delivery vehicles in form of solubilizers, wetting agents, etc.

They constitute of a hydrocarbon segment which is considered as the hydrophobic region that is mainly aliphatic chain, and a polar region that could be anionic, cationic, non-ionic or zwitterionic (Kumar & Singh, 2016).

Surfactants when placed in hydrophilic media until they reach a critical concentration value, they align their structure where the hydrophobic region of the surfactant come close together and therefore the polar region will face the hydrophilic part of the media forming a structure known as the micelle. The concentration at which micelles begin to form is known as the Critical Micelle Concentration (CMC). These micelles have

varying polarities, which indeed assists the solubilization of poorly soluble drugs by incorporating them inside those micelles (Vinarov et al., 2018).

As previously mentioned, there are several types of surfactants, Polysorbate-80 or Tween-80 (Polyoxyethylene sorbitan monooleate), which was used in the current research as seen in (Figure 2.4), is known as hydrophilic nonionic surfactant, that is formed by the reaction of sorbitan fatty acid ester with ethylene oxide. It has an HLB (Hydrophilic- Lipophilic Balance) value of 15 and CMC of 13-15 mg/liter. It is used as a solubilizing agent in concentrations up to 2% and occurs as a yellow oily liquid (Rowe et al., 2006) (Purcaru et al., 2010).

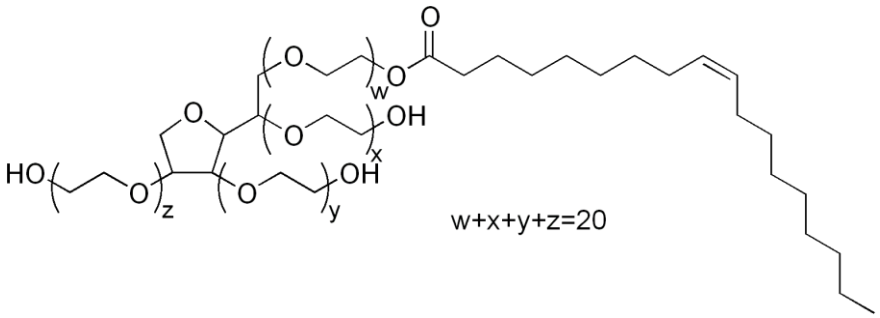

Figure 2.4: Tween-80 Structure.

2.3 Factors Influencing Solubility and Dissolution

There are several factors that can affect the solubility and dissolution of the drugs. In the matter of fact, factors influencing solubility and dissolution are almost the same, since in order to modify the drugs dissolution, modification of the solubility factors are required (Shahrin, 2013).

To begin with, the drugs characteristics, such as particle size is quite important. It is known that as the particle size decreases, the surface area increases and therefore more of the drug will be available to the solvent hence the solubility increases. Due to these criteria, Nimesulide used in the current research was supplied in the micronized form (Gaikwad et al, 2014).

Secondly, Organic drugs mainly encounter an endothermic dissolution, therefore, an increase in temperature will result in solubility enhancement, since more energy will be available to break the solid particles and allow them to solvate in the medium solvent. In dissolution, temperature plays an important role but since the conditions should resemble the body temperature, the temperature is always fixed at 37±ºC (Shahrin, 2013) (Kadam et al., 2013).

Moreover, the acid-dissociation constant pKa and pH are important for weak acid or basic drugs, since their solubility is mainly dependent on them. Therefore, variable solubilities are observed within the body (e.g. stomach and intestines or in the fasting or fed state). For instance Nimesulide has a pKa value of 6.4 (acidic nature) therefore its solubility increases mainly by increasing the pH of the medium (Shahrin, 2013) (Vemula et al., 2010)

Alternatively, there are also certain factors that affect the dissolution process. Generally, dissolution occurs in two consecutive stages. Primarily, an interfacial interaction occurs between the solid and liquid phase, which releases the solute molecules and secondly, these molecules will be transported from the interface to the bulk medium through diffusion. Thus, this process and the factors affecting it can be described in Equation (2.1) is called the Noyes-Whitney equation (Taylor & Aulton, 2013).

$$dm/dt = \frac{DA(Cs-C)}{h} \qquad (2.1)$$

Where (dm/dt) is the rate of dissolution of the drug particles:

(D) The diffusion coefficient of the drug in solution in the gastrointestinal fluids.

(A) The effective surface area of the drug particles in contact with the gastrointestinal fluids.

(h) The thickness of the diffusion layer around each drug particle.

(Cs) The saturation solubility of the drug in solution in the diffusion layer.

(C) The concentration of the drug in the gastrointestinal fluids (bulk concentration).

Over here, this model has the following assumptions taken into consideration. Firstly, the drug should be dissolved uniformly from all surfaces of the particles. Secondly, the particles are assumed to be spherical. Thirdly, the thickness of the diffusion boundary layer remains constant and finally the thickness of the diffusion boundary layer and the saturation solubility are known to be independent of particle size (Hoener & Benet, 1996).

When the volume of the solvent is large or when the dissolved drug (solute) is removed from the medium at a rate faster than the rate of solution entry, then the C is approximately zero, so Cs -C = Cs, this is called as sink conditions. But when C accumulates {C > (CS/10)}, then this is not considered as sink conditions.

Also when Cs = C, then the medium is saturated and the dissolution is zero (Taylor & Aulton, 2013).

The concentration of drug in solution at the bulk of the gastrointestinal fluids, C, will be influenced by the rate of removal of dissolved drug by absorption through the gastrointestinal blood barrier and by the volume of fluid available for dissolution, which in turn will be dependent on the location of the drug in the gastrointestinal tract and the timing with respect to meal intake (Hoener & Benet, 1996).

According to Noyes-Whitney equation, in (Table 2.2) as quoted from (Shahrin, 2013), it usually sums up the physicochemical characteristics, the in-vitro and in-vivo factors that may affect the drugs dissolution rate.

Table 2.2: Factors affecting dissolution rate (After (Hoener & Benet, 1996)).

Parameter	Physicochemical characteristic	Physiological variable-in vivo factor	In vitro factor
A	Particle size	Presence of surfactants	Presence of surfactants
h		GIT motility	Stirring rate System hydrodynamics
D	Molecular size	Viscosity of gastrointestinal fluids	Viscosity of medium
S	Hydrophilicity Crystalline state	pH surfactants	pH surfactants
C_b		Volume of gastrointestinal fluids	Viscosity of medium

2.4 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 dissolution, solubility and intestinal permeability. 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 ºC.

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 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 et al., 2017).

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).

Powder Flow: Powder flow is defined as the ability of the powder to flow in a desired manner in a specific piece of equipment. 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 P. , 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 are several methods utilized that determine the flow characteristics of our powder, most importantly these include:

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 $\theta = (h/r)$, 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 $\leq 30°$, it is free-flowing whereas $\geq 40°$ 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 2.3).

Table 2.3: Describes the angle of repose ranges for powder flowability (After (Geldart et al., 2006)).

Flow Property	**Angle of repose (degrees)**
Excellent	25-30
Good	31-35
Fair- aid not needed	36-40
Passable- may hang up	41-45
Poor, must agitate vibrate	46-55
Very poor	56-65
Very , very poor	≥65

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 (2.2 and 2.3) (Shah et al., 2008).

$$\text{Compressibility index} = \frac{\text{Tapped density} - \text{Bulk density}}{\text{Tapped density}} * 100 \quad (2.2)$$

$$\text{Hausner's ratio} = \frac{\text{Tapped density}}{\text{Bulk density}} \quad (2.3)$$

Table 2.4: Describes the compressibility index and Hausner ratio ranges (Taylor & Aulton, 2013).

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

Additionally, hygroscopic materials should be controlled carefully since moisture level changes can have a great influence on various important parameters such as compatibility, chemical stability and flowability. For instance, when water is absorbed on the candidate drug or even on the available excipients, this may induce hydrolysis which alternatively affects the stability of the compound. Therefore, hygroscopisity of the material should be tested in the preformulation studies (Vilegave et al., 2013).

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).

Additionally, 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.

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, where as 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. 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.

It is essential to be able to quantify the materials elasticity, plasticity and brittleness in order to understand the compaction behavior of a certain material. Such methods include using the compaction simulator to produce Heckel plots.

Heckel equation has been used universally to describe the compaction properties of powders. It explains the relationship between pressure applied and the volume bed of the powders tested. It can be calculated using the following Equation (2.4):

$$\ln \frac{1}{1-D} = kP + A \qquad (2.4)$$

Where, D is the relative density, which is the ratio of the apparent density to the true density, K is determined from the slope of the Heckel plot, P is the pressure and A is determined by the intercept of the extrapolation of the straight portion of the line. The yield pressure can be obtained from the reciprocal of the slope and used to determine the deformation of the materials (Çelik M. , 1992).

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).

2.6 Formulation Design for Tableting

In order to produce any dosage form, a formulation design is usually required. Formulation design constitutes excipients and process formulation. The suitable excipients and processes are chosen depending on the API properties.

2.6.1 Tablet Process Formulation

Tablets can be prepared either by compression or molding and nowadays compressed tablets resemble the vast majority of tablets being produced, since a number of physical requirements are satisfied through this type of production such as hardness, thickness, weight uniformity and friability. Now depending on the properties of the pharmaceutical active material, the excipients used and the combination characteristics of both the active pharmaceutical material and the excipients, the method of tablet production can be determined. Traditionally, there are two main processing technologies used, these include direct compression and granulation (Harbir, 2012).

Granulation is considered to be a general description for particle enlargement process where the particles will be agglomerated whilst the integrity of the original particles will be retained. There are two types of granulation, wet and dry granulation. Usually, the addition of a polymeric binder which is mainly hydrophilic in nature is involved in the granulation process so it allows the sticking of the individual particles together. In wet granulation, the binder is in a solution form whereas dry granulation has a dry binder in powder form added.

There are several reasons behind the use of granulation. First of all, in order to render the powder to be free flowing which is considered to be the main rationale behind the granulation process. Secondly, to increase the bulk density of the powder; therefore, to guarantee that the die is filled with the required volume of powder. Thirdly, is to provide uniform mixtures by enhancing the mixing homogeneity and to reduce the likelihood of segregation. Fourthly, the drug's compression characteristics will be improved and the rate of drug release can be controlled. Finally, it ensures that a homogeneous color distribution is attained and therefore improves the tablet appearance and eventually reduces dust liberation (Kara et al., 2009) (Lieberman et al., 1989).

2.6.1.1 Dry Granulation

In this method, the active component, lubricant and in some cases a diluent are mixed together (Freitag, 2004). It is required that either the active component or the diluent to contain cohesive characteristics (Grote, 2018). Then, primary powder particles are aggregated by using high pressure (Gupte, 2017).
There are two major used procedures:

1. Slugging, which is the process of obtaining a big tablet by using a heavy duty tableting press
2. Roller compaction, which is the process of compressing powder between 2 rollers in order to make a sheet of the substance (Herting M. G., 2007), (Kleinebudde, 2004).

After that, appropriate milling methods are used on the obtained products to make granular substances, after that they are divided based on their size fraction and the required particles are isolated (Shanmugam, 2015).
Dry granulation technique has many advantages, such as requiring less phases, however the main steps such as measuring the weight, blending, slugging, dry screening, lubrication, and compressing the tablet remain a part of the process, also components avoid being exposed to granulation liquid and heat that is usually needed for the granulated substance to be dried (Herting M. G., 2007).
Dry granulations could be used for medications that have poor compressible properties after wet granulation, for medication that are affected by moisture and heat and for medications that contain enough binding or cohesive characteristics (hang, 2008).

2.6.1.2 Wet Granulation

This method includes the mixing of a granulating liquid with a mixture of dry primary powder components to obtain a wet mass that compose bigger agglomerates called granules. When granule enlargement is reached, the wet massing step is stopped, and the obtained granules are dried, at that time the components dissolved in granulation liquid will establish firm bond that retain the particles together (Benali, 2009). Usually, a

binder which has a role in constantly keeping the particles attached. Lastly, dried granules could be milled to obtain the required particle size (Horisawa, 2000).

This method is used more than any other method to prepare a tablet because it provides a higher chance of achieving all of the needed physical properties for a well compressed tablet (Faure A. G., 1999). The granulating liquid includes a solvent which has to be safe and volatile in order to be excluded through drying. Commonly used fluids contain either water, ethanol, or isopropanol (Faure A. Y., 2001). Water is commonly chosen because it costs less and for environmental reasons (Kiekens, 2000). On the other hand, water may affect drug stability and if used, drying takes more time compared to other solvents. As a result, the procedure will take more time to be done which may also affect stability due to the of the prolonged duration of facing heat (Schaefer, 1990).

The main disadvantage of this method is that there are a lot of divided phases and it requires a long period of time and more effort to be done, particularly when large quantities are made. Also, in this method, the ingredients of the formula are exposed to high temperatures and granulating fluid which are required to dry the granules (Rajniak, 2009).

Wet granulation can be done in high shear apparatus or by using fluid bed technology. The resulting granules characteristics are based on the qualities of the used materials and the procedure restrictions for granulation (Lipps, 1994). The utilized apparatus is chosen according to the amount or size of the lot and the amount of active ingredient compared to complete tablets weight. Wet formulation could be achieved through one of these apparatus: low Shear mixers, high Shear mixers, fluid-Bed granulators, spray dryers, or extruders and spheronizers.

According to the preformulation studies conducted on Nimesulide, the process formulation chosen was Direct Compression (DC), another type of process formulation.

2.6.1.3 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 there 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).

Advantages of Direct Compression: (Iqubal et al, 2014)

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.

Disadvantages of Direct Compression: (Lieberman et al., 1989)

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.

2.7 Excipients Formulation

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).

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).

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. In spite of excipients being classified according to their primary functions, there are several excipients that are considered to be multifunctional. For instance, the same excipient may act differently when present at different concentrations (Patel et al., 2011).

In the current research, the excipients utilized with Nimesulide formulation includes, filler, binder, disintegrant and lubricant, in which they were processed by the Direct Compression method. Therefore, only directly compressible excipients were used in the research and will be highlighted in this section.

2.7.1 Diluents

They are excipients added to increase the bulk of low dose potent drug formulations, in order to increase the tablet size and provide better handling of the dosage form by the patient and by the manufacturer. 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).

There are soluble (e.g. lactose, sucrose) and insoluble fillers (e.g. starch, microcrystalline cellulose). Nimesulide was formulated using a combination of lactose (Flowlac-100) and microcrystalline cellulose (Avicel-102) as the filler of choice (Darji, et al., 2018).

There are two types of lactose, the crystalline and amorphous lactose. Flowlac-100 is spray-dried lactose, which is composed of 80-90% of pure alpha-lactose monohydrate and 10-20% of amorphous lactose. The crystallized lactose could be anhydrous or

monohydrate, where the former is used in direct compression, while the latter is used in wet granulation. 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).

Microcrystalline cellulose has several grades, which includes Avicel, Emcocel and Vivacel. Mainly the differences between the grades are due to the differences in there particle size and moisture content level. Avicel-102 is known for its use mainly in direct compression. The concentration in which MCC behaves as a tablet filler is considered to be in the range between 20-90% (Rowe et al., 2006).

2.7.2 Binders

Binders normally intend to hold the tablet ingredients together in which they mainly impart cohesion characteristics that enhance the mechanical strength and flow properties of the tablets and granules powder mix.

Binder classification mainly depends on their application. For instance, they are either solution binders (e.g. dissolved in solvent in wet granulation) or dry binders added to the powder mix in wet granulation or direct compression (Darji, et al., 2018) (Joneja et al., 1999).

Povidone (Kollidon-30) is white, fine hygroscopic powder that shows an enhancement in the dissolution of poorly water soluble drugs from the solid dosage forms. The applied concentrations used in the formulations to give the binder effect are known to be in the range of 0.5-5% (Rowe R. C., 2006).

2.7.3 Disintegrants and Superdisintegrants

These types of excipients usually function in a way that promotes the disintegration of the tablet. They may act by facilitating the water uptake into the tablet pores or through swelling, either way this leads to tablet rupturing and disintegration.
Moreover, disintegrants who swell up dramatically upon exposure to water are known to be superdisintegrants, an example is Crosscarmellose (Remya et al, 2010).

Kollidon CL, white, finely divided free flowing hygroscopic powder is used in direct compression and wet granulation within a concentration range 2-5%. It is known to be as water-insoluble superdisintegrant, that can be used as a solubility enhancer (Rowe R. C., 2006) (Jagtap et al., 2019)

Sodium Starch Glycolate or (Primojel) is white free-flowing very hygroscopic powder, used in either direct-compression or wet-granulation processes. The usual concentration employed is between 2-8%, with an optimum concentration about 4%. The process occurs by rapid uptake of water then followed by rapid and enormous swelling. The superdisintegrant effect of Primojel is usually not affected by the presence of lubricants or high compression pressure (Rowe R. C., 2006) (Mangal et al., 2012).

2.7.4 Lubricants

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.

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).

2.8 Compaction Simulator

There are several types of equipment that provide the powders compaction in the pharmaceutical area and they mainly include single-press, rotary-press and the compaction simulator. Nimesulide was directly compressed using the compaction simulator.

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 M. &., 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).

2.9 Tablets Tests

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.

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.

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).

   When Nimesulide was prepared, each tablet was prepared separately, therefore weight variation was measured. 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. **Disintegration:**

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.

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).

3. **Dissolution:**

The main objective behind performing this in vitro dissolution testing is to obtain a realistic prediction or correlation with the product's in vivo bioavailability. 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).

According to the European pharmacopeia, the apparatus used for solid dosage forms such as tablets will mainly utilize the paddle or basket apparatus unless otherwise authorized and justified. Depending on the monograph of the specified active pharmaceutical material, the volume and the composition of the dissolution medium will be placed in the dissolution vessel and its temperature set at 37 ± 0.5 °C. The dosage forms will be placed either at the bottom of the vessel (paddle) or in the basket before rotation commences.

Apparatus-I: Paddle Apparatus:

As seen in (Figure 2.5), 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. 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 (European Pharmacopoeia, 7th edn, 2011).

Apparatus-II: Basket Apparatus:

The apparatus assembly contains the following as seen in (Figure 2.6):

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 (European Pharmacopoeia, 7th edn, 2011).

4. Friability of Uncoated Tablets:

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).

5. Hardness of Tablets:

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).

6. **Thickness of Tablets:**

   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).

2.10 Quality by Design 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 & Mesut, Quality by design (QbD) for pharmaceutical area., 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.

The authorities and experts of pharmaceutical industries in USA, Japan and Europe were gathered and developed a forum to harmonize the pharmaceutical product technical requirements in these three regions to form the International Conference on Harmonization (ICH) guidelines. It is composed of several sections, and the main sections regarding QbD are implied in Q8, Q9 and Q10 guidelines (Aksu B., 2014).

The QbD concept was first introduced by Q8 guideline in 2005, in which QbD was defined as "a systematic product development approach that begins with pre-defined objectives and emphasized understanding of the product and process based on firm science and quality risk management" (Q8 (R2) Pharmaceutical Development,, 2009). In this guideline, a control strategy is proposed to ensure that the Target Product Profile (TPP) is achieved in a reproducible way. Mainly, the control strategy focuses on the variability of the critical sources, such as certain raw materials. As a result, the control strategy includes all input materials, in-process testing such as off-line, at-line or on-line and also unit operations and the quality control tests on the final product. Usually, the design of such control strategy is mainly influenced by the level of process understanding (Lionberger et al., 2008).
Moreover, Q8 guideline explains the design space concept as “the multidimensional combination and interaction of input variables (e.g. material attributes) and process parameters that have been demonstrated to provide assurance of quality.”

Another ICH guideline Q9 is Quality Risk Management, it points out what is a risk, the evaluation of such risk and where such Quality Risk Management can be applied. There are variety of tools such as Failure mode effects analysis (FMEA), that are used for such assessments and they can be used at various stages of the pharmaceutical operations (Aksu et al., 2013).

Finally, ICH guideline Q10 is published mainly to regulate the pharmaceutical product manufacturers quality management system by achieving quality standards in design and risk assessment during the life cycle of the product (Aksu B., 2014).

ICH Q10 defines a control strategy as "a planned set of controls derived from current product and process understanding that assures process performance and product quality.

The controls can include parameters and attributes related to drug substance and drug product materials and components, facility and equipment operating conditions, in process controls, finished product specifications and the associated methods and frequency of monitoring and control." (Jain S. , 2014)

As a result, control strategy guarantees that the process is preserved within the boundaries illustrated by design space. The next section describes the several steps implied in the QbD process and development.

2.10.1 Quality by Design Approach Steps

Briefly, this approach mainly aims to produce a drug product that fulfils the required patient needs by building the quality in the product instead of testing it as the conventional method. This approach is mainly based on science, either from previous studies or from the literature on the raw materials and type of process used. There are several steps implemented through QbD as described in (Figure 3.1).

The first step includes defining the design targets of the product this includes the Target Product Profile (TPP) and Quality Target Product Profile (QTPP).

Target Product Profile (TPP): In this profile, information containing the main purpose of the drug development program and the development process will be highlighted. They contain specific information that is required to be placed on the drug label such as use, safety and efficacy.

Quality Target Product Profile (QTPP): Mainly in this profile, a summary on the attributes of the product that may dictate its quality and that could support the clinical efficacy and safety are implemented. The quantitative targets for the drug attributes, such as solubility, potency, impurity and stability will be defined. Also, specifications

such as the dosage form, method of application, packing criteria, appearance and the diagnosis will be included. Moreover, the release profiles and other requirements on the product-specific performance are also available (Mesut et al., 2015).

The second stage is related mainly to the formulation inputs. For instance, knowledge on the active pharmaceutical material and the excipients used along with the process operations will be gathered and analyzed. This science based information will allow us to predict the critical parameters implied in the whole manufacturing process and the Critical Quality Attributes (CQA) for the product.

The CQAs are the factors that mainly affect the product quality, in which they are either physical, chemical or biological attributes implied to be in a certain limit. They could be about the active ingredients, excipients and the finished product. Mainly, solid dosage form CQAs usually has an effect on the product purity, stability, drug release and strength. In other words, anything that may affect the product efficacy and quality is considered critical and needs to be monitored efficiently (Aksu B, 2015).

Indeed every product requires raw materials and certain process in order to be produced. Therefore, the third stage is mainly to assess the material attributes and process parameters and link them to the CQAs, in order to obtain the Critical Process Parameters (CPP) and Critical Material Attributes (CMA) through risk assessment analysis.

CPP is a process parameter, in which any variability in it shows an effect on the CQAs of the drug product and thus it should be controlled to guarantee the production of a process with desired quality. On the other hand, CMAs are physical, chemical or biological property of an input material that should be in a proper limit to ensure the products quality (Aksu B, 2015).

Fourthly, after establishing the Critical Material Attributes (CMA) and the Critical Process Parameters (CPP), these factors will be considered as (inputs), and by knowing the CQAs of the final product (outputs), a design space can be implemented in which the formulator can function in any area that is known to be within the design space.

Mainly all pharmaceutical formulations are produced through various unit operations. For instance, direct compression requires only two steps (mixing and compression),

while wet granulation require several steps. In such cases, the outputs obtained from one step are considered to be the inputs of the second step (Mesut et al., 2015).

Finally, the input material controls, monitoring and process controls, and design space, should be controlled by a control strategy which includes online/inline, offline or at line strategies (Mesut et al., 2015).

This approach allows the formulators to discover more optimized formulations and therefore enhance the product development since there are no certain specifications needed to be followed except for the design space and any post-approval changes can be easily conducted if it still implies within the design space in which any change within the design space will not be considered as a change and does not require any regulatory approval process, this in turn saves time and energy unlike the conventional method.

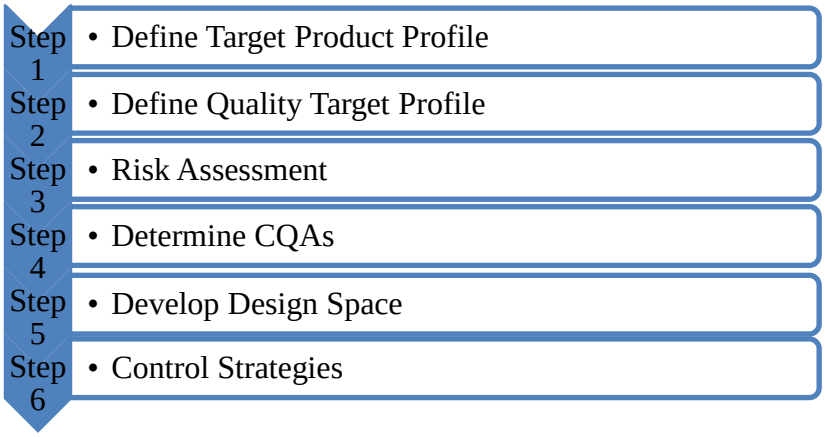

Figure 3.1: Summary of Quality by Design approach.

CHAPTER 3: MATERIALS and METHODS

3.1 Materials

The following materials were used in the study:

Nimesulide (Sanovel Ilac), sodium hydroxide (Merck, Lot# 1.06482.1000), di-sodium hydrogen phosphate (Merck, Lot# 1.06580.1000), potassium dihydrogen phosphate (Merck, Lot# 1.04873.1000), citric acid (Merck, 1.00241.5000), Tween®80 (Merck, Lot# 8.22187.1000), Flowlac®100 (Meggle, Lot# 0846), Avicel®102 (FMC Lot# 71434C), magnesium stearate (Lot# C113930), Primojel (DFE.Pharma), Kollidon®30 (BASF, Lot# 73300675L0), Kollidon®CL (BASF, Lot# 01117168E0) and water was used as distilled as seen in (Figure 3.1).

Figure 3.1: Excipients and chemicals utilized

3.2 Method

3.2.1 Buffer preparation

According to EP , the following phosphate buffers were prepared in different pH

1. pH 4.5: Dissolve 6.80 g of potassium dihydrogen phosphate in 1000.0 mL of water.
2. pH 6.0: Mix 63.2 mL of a 71.5 g/L solution of disodium hydrogen phosphate and 36.8 mL of a 21 g/L solution of citric acid.
3. pH 6.8: Mix 77.3 mL of a 71.5 g/L solution of disodium hydrogen phosphate with 22.7 mL of a 21 g/L solution of citric acid.
4. pH 7.0: Mix 82.4 mL of a 71.5 g/L solution of disodium hydrogen phosphate with 17.6 mL of a 21 g/L solution of citric acid.
5. pH 7.4: Add 250.0 mL of 0.2 M potassium dihydrogen phosphate to 393.4 mL of 0.1 M sodium hydroxide.

3.2.2 Analytical study for Nimesulide

In this section, the calibration curves were determined and a solubility study for Nimesulide was conducted.

a. Calibration curves

Phosphate buffer solutions were prepared at pH (7.4, 7.0, 6.8, 6.0, and 4.5) with various Tween®80 concentrations ranging from (0.5-2%) as seen in (Table 3.1). The pH was measured using Mettler Toledo pH meter as shown in (Figure 3.2)

Stock solutions were prepared by dissolving 5mg of Nimesulide in 100 ml of buffer solutions. The buffer solutions contained, (pH 7.4), (pH 7.4 with 0.5% Tween-80), (pH with 0.5% Tween-80) and (pH 6.8 with 1% Tween-80).

The stock solution had its λmax determined by Shimadzu UV-1800 spectrophotometer as demonstrated in (Figure 3.3). The λmax was measured according to (Table 3.2). Then, the solution was subjected to serial dilutions and had its absorbance measured in the range of (0.1-1 A). According to the R^2 value, the linearity of the study was evaluated.

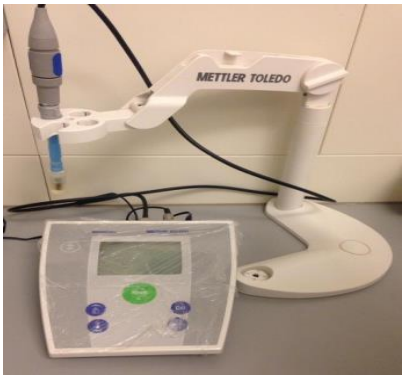

Figure 3.2: pH meter(Mettler Toledo)

Figure 3.3: UV/Vis spectrophotometer (Shimadzu UV-1800)

Phosphate Buffer pH	**Tween-80 concentration (%)**				
	0	0.5	1	1.5	2
7.4	*	*			
7.0	*	*			
6.8	*	*	*		
6.4			*	*	*
6.0				*	*
4.5					*

***** The concentration of Tween-80 used in each phosphate buffer

Table 3.1: Concentration of Tween-80 in each buffer media

b. Solubility study

0.5 g of Nimesulide was added in 100 ml phosphate buffer 7.4 solution in an erlenmeyer flask, closed tightly with paraffin foil and placed in water bath of 37 °C and stirred at 700 rpm using a small magnetic stirrer. Samples were taken after three hours for 24 hours. The sample was stopped stirring for an hour before sampling to get a clear sampling area. Each sample was then diluted and analyzed using the spectrophotometer

at λmax 393nm to obtain the absorbance. Shaking continued until two consecutive absorbances were obtained the same. After that, the saturation solubility was calculated.

Medium	**λmax (nm)**
pH 7.4	393
pH 7.4 with 0.5% Tween-80	397
pH 7.0 with 0.5% Tween-80	397
pH 6.8 with 1% Tween-80	396

Table 3.2: λmax values in several phosphate buffer medias

3.2.3 Powder Controls

3.2.3.1 Particle Size Analysis

a. Light Microscope: The powders morphologies of Nimesulide, Kollidon-30, Primojel and Magnesium stearate were tested by Yildiz Technical University.
b. Laser diffraction method: It was provided from Sanovel company by Malvern laser diffractometry as dry method and the particle size distribution was examined.

3.2.3.2 Melting point

The melting point of Nimesulide was determined by Mettler Toledo FP90 Central Processor as seen in (Figure 3.4).

Figure 3.4: Central Processor (Mettler Toledo)

3.2.3.3 Infrared Spectrum (IR)

The data was provided from Sanovel ilac API company.

3.2.3.4 Brunauer-Emmett-Teller (BET)

The surface area was determined for two formulations containing no binder (Nimesulide, Flowlac-100, Avicel-102 and Magnesium stearate) and with 5% binder (Nimesulide, Flowlac-100, Avicel-102, Magnesium stearate and 5% Kollidon-30). This test was performed by Yildiz Technical University.

3.2.3.5 Powder Densities

Nimesulide, Flowlac®100, Avicel®102 and Kollidon®30 had the following tested.

a. **Bulk density:**

   50g of each powder was weighed and placed carefully without shaking in the measuring cylinder according to EP and the volume (ml) was recorded.

b. **Tapped density:**

   50g of each powder was placed in the measuring cylinder and the initial volume was recorded. According to EP, the powder was mechanically tapped by Erweka SVM (195 SVM 203) as seen in (Figure 3.5) and volume readings were taken until little further volume change was observed.

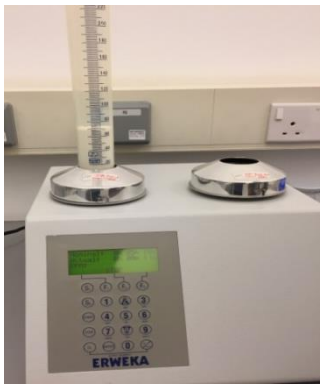

Figure 3.5: SVM machine (Erweka).

From both bulk and tapped densities Carr's Compressibility index and Hausner’s ratio were calculated as seen in equations (2.2) and (2.3).

c. **True density:**

This test was performed by Yildiz Technical University using the helium pycnometry.

3.2.4 Formulation Design

The formulations prepared had fixed amount of Nimesulide as dose (100 mg). The filler used was Flowlac®100 as a soluble filler and Avicel®102 as an insoluble filler, they were placed in a ratio of 3:1 respectively. The Magnesium Stearate used also was fixed as 4 mg for all formulations.

The changed parameters were the amount of binder (Kollidon®30 2 and 5%), the type and amounts of superdisintegrants (Primojel 2 and 5%) and (Kollidon®CL 2 and 5%) and finally the compression force (5 and 10 KN).

There were 30 formulations prepared. For each formulation gradual mixing of the expients was applied. The specified amount of filler and Nimesulide were mixed for 5 minutes, then the binder and superdisintegrants were added and mixed for another 5 minutes and finally, the magnesium stearate was added and mixed for 5 minutes.

Mixing was done in plastic packet and then the powder was directly compressed at two forces(5and 10 KN) using Stylcam Compaction Simulator R 200 as seen in (Figure 3.6) and (Table 3.2).

Figure 3.6: Stylcam Compaction Simulator R 200.

Table 3.3: The formulation composition of tables.

Formulation	Nimesulide (mg)	Lactose (mg)	Mcc (mg)	Kollidon 30 (mg)	Primojel (mg)	Kollidon CL (mg)	MgSt (mg)
K00	100	225	75	0	0	0	4
K0P2	100	225	75	0	8	0	4
K0P5	100	225	75	0	20	0	4
K0K2	100	225	75	0	0	8	4
K0K5	100	225	75	0	0	20	4
K20	100	225	75	8	0	0	4
K2P2	100	225	75	8	8	0	4
K2P5	100	225	75	8	20	0	4
K2K2	100	225	75	8	0	8	4
K2K5	100	225	75	8	0	20	4
K50	100	225	75	20	0	0	4
K5P2	100	225	75	20	8	0	4
K5P5	100	225	75	20	20	0	4
K5K2	100	225	75	20	0	8	4
K5K5	100	225	75	20	0	20	4

3.2.5 Tablet Quality Controls

Throughout this study, weight variation, hardness, disintegration, dissolution and friability were tested for our formulations and two Turkish marketed products (ND and NS).

a. Weight variation

According to EP, the ten tablet specimens (n=10), were weighed individually and had their weights recorded. Then the average weight of the tablets was determined and the % deviation was calculated.

$$\text{Deviation (\%)} = \left(\frac{\text{tablet weight} - \text{average tablet weight}}{\text{average tablet weight}}\right) * 100 \qquad (3.1)$$

b. Hardness measurement

The test was preformed according to EP using Erweka hardness tester machine (265 TBH 225). The apparatus constitutes mainly of two jaws that face each other and one of them usually moves towards the other. The test is carried on 3 tablets (n=3), each tablet will be placed between the jaws and the force required to break the tablet was measured as (N) as seen in (Figure 3.7).

Figure 3.7: Hardness tester (Erweka).

c. Thickness

The thickness was measured by automatic caliper (0-150mm TCM) as shown in (Figure 3.8).

Figure 3.8: Digital Caliper (TCM).

d. Disintegration

The test was performed using Erweka disintegration tester (240 ZT 322). During the procedure, one tablet is placed in each of the six tubes and a plastic disc is added on top to prevent the tablets from getting out of the tubes. Then this assembly will be immersed in a beaker containing water unless otherwise specified in the individual monograph of the active ingredient. Then the test is run and the time for the particles required for the tablet to pass through the mesh was recorded as seen in (Figure 3.9).

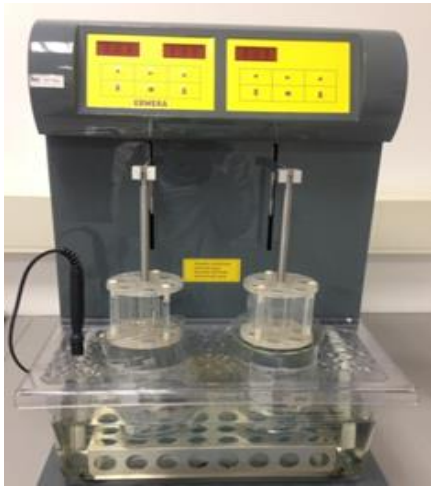

Figure 3.9: Disintegration tester (Erweka).

e. Dissolution

ND and NS market products and our formulations had their dissolution tested according to EP using apparatus-I paddle. The dissolution medium used for the marketed products was phosphate buffer pH 7.4 (without Tween-80 and with 0.5% Tween-80) and pH 6.8 (without Tween-80 and with 1% Tween®80) at 37 ±5ºC.

The dissolution medium used for our formulations was (pH 7.4 with 0.5% Tween-80). The volume of media placed in the vessel was 900ml (Purcaru et al., 2010).

The test was run at two rpm (75 and 50) for ND and NS, while our formulations were run only at 75 rpm.

The sampling criteria was carried at specified time intervals (after 5, 10, 15, 30, 45 and 60 minutes), where the sample was withdrawn from a midway zone that is between the top of the paddle and the surface of the dissolution medium, provided that it is not less than 1 cm from the vessel wall. The obtained sample was filtered using an appropriate filter and then analyzed by the UV/Vis-spectrophotometer using the λmax specified for each medium as described in (Table 3.1). The test was conducted using Erweka dissolution tester as shown in (Figure 3.10).

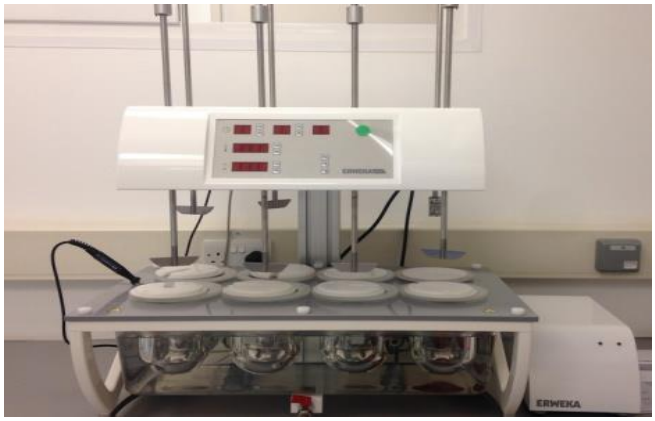

Figure 3.10: Dissolution tester (Erweka).

f. Friability

Friability test was conducted according to EP using Erweka friability tester as determined in (Figure 3.11), the tablets were weighed and had their average weight calculated before placing them into the drum, following that, the tablets were rotated in the drum for 100 times at 25 rpm. Afterwards, the tablets were dusted very well and had their average weight recalculated. Then the percentage weight loss was determined.

Figure 3.11: Friability tester (Erweka).

3.2.6 Quality by Design approach

3.2.6.1 Target Product Profile (TPP)

Table 3.4: Target Product Profile of Nimesulide.

Specification	Target Product Profile
Dosage Form	Immediate Release Tablet (Orally)
Dosage Strength	100 mg
Pharmacological Action	NSAIDs

3.2.6.2 Quality Target Product Profile

Table 3.5: Quality Target Product Profile of Nimesulide.

Specification	Quality Target Product Profile
Tablet weight	444 ≤ weight mg ≥ 404
Weight variation	±5%
Disintegration	Less than 2 minutes in distilled water
Dissolution	≥ 85% in 30 minutes
Hardness	60-80 N
Friability	< 1%
Moisture content	Less than 1%

The CQAs were then determined from previous knowledge as dissolution, disintegration, and tensile strength of the tablets. The results obtained from quality control tests were applied in umetric MODDE software as QbD approach and the reference product chosen was Nimes.

3.2.6.3 QbD Software

The program used in our study is MODDE - (MODeling and DEsign) is a Windows program for the generation and evaluation of statistical experimental designs.
Methods of statistical experimental designs have evolved since the pioneering work of Fisher in 1926. These methods, further refined by Box, Hunter, Scheffé, Tagushi, and others, provide users with a powerful methodology for efficient experimentation.

The experimental design is how to conduct and plan experiments in order to extract the maximum amount of information from the collected data in the presence of noise. The basic idea is to vary all relevant factors simultaneously, over a set of planned experiments, and then connect the results by means of a mathematical model. This

model is then used for interpretation, predictions, optimization and identifying a design space.

After entering in Design wizard first thing we defined factors (Input of the experiment) by inserting factor's name, Type of factor (Quantitative, Quantitative multilevel, qualitative, Formulation or Filler), and factor's range. Then, the responses were defined by inserting the response name, abbreviation, units, selecting type of response (Regular and Derived) and limits. In this study, we didn't select an objective from the program because we are creating our own.

After that, the worksheet with input and output of the experiment was filled then it was clicked on analyzed wizard .The program will show many plots and these plots occur for each response. Theses plots include:

1. Replicate plot:

   The replicate plot shows the variation in results for all experiments for quick raw data inspection. Repeated experiments appear in a different color connected by a line. The ideal outcome is that the variability of repeated experiments is much less than the overall variability. Experiments deviating significantly from the others should be checked.
2. Histogram plot: The histogram shows the shape of the response distribution and is used to determine if a transformation is needed. The desired distribution is a "bell shaped" normal distribution. A proper estimate of the distribution requires a minimum of 11 observations. By selecting an appropriate transformation a non-normal distribution might be transformed to normal distribution. In general, normally distributed responses will give better model estimates and statistics.
3. Coefficient plot: The coefficients plot shows the significance of the terms in the model.
4. Summary plot: A summary of the basic model statistics in four parameters; 1 is perfect 100%. Model validity is a test of diverse model problems. A value less than 0.25 indicates statistically significant model problems, such as the presence of outliers, an incorrect model, or a transformation problem.

Reproducibility is the variation of the replicates compared to overall variability. A value greater than 0.5 is warranted. Correct model tuning like removing non-significant model parameters or selecting the appropriate transformation results in higher summary statistics. The best and most sensitive indicator is Q2.

5. Residuals Normal Probability plot: This plot shows the residuals of a response vs. the normal probability of the distributions if all points are on a straight line on the diagonal, the residuals are normally distributed noise. This is the ideal result. Points outside the red lines indicate outliers that should be checked. A curved pattern indicates non modeled quadratic relations or incorrect transformation of the response. DF <5 can result in strange patterns. Deviating experiments shall be compared with the same deviation in the "Observed vs Predicted plot", a significant deviation can be very minor in that perspective.

R2 Shows the model fit. A model with *R2* of 0.5 is a model with rather low significance. Q2 Shows an estimate of the future prediction precision. Q2 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.

After finishing and reviewing all the summaries of the responses.We chose the Fit model Multiple Linear Regression (MLR), clicked on Design space wizard On program , and chose 4D Design space plot to show the probability of failure percentage (%) for the shown factor combinations. The lowest probability of failure point was picked from the graph and tested it.

CHAPTER 4: RESULTS and DISCUSSION

4.1 Analytical Study

As stated by the FDA, that if the product dissolution is pH dependent then, dissolution should be done in at least three medias to resemble the GIT conditions (e.g. pH 1.2, 4.5, 6.8) (Chen et al., 2001). In the current study, in order to choose the appropriate amount of Tween®80, at each pH, various amounts were applied to observe the minimum percentage of tween required to dissolve Nimesulide at that particular pH. The results are shown in (Table 4.1).

Table 4.1: pH effect on Nimesulide solubility

Phosphate Buffer	Tween 80 %	Solubilization	Final Appearance
7.4	0	+	Deep yellow
	0.5	+	
7.0	0	-	Yellow with ppt
	0.5	+	Medium yellow
6.8	0	-	Light yellow with ppt
	0.5	-	Yellow with ppt
	1	+	Deep yellow
6.4	1	-	Very light yellow
	1.5		
	2		
6.0	1.5	-	Very light yellow
	2	-	
4.5	2	-	Very slight yellow tint

(+) : soluble, (-) : not soluble

Nimesulide dissolved in pH 7.4 without using Tween and when 0.5% was added the solubility was faster, which would enhance the dissolution release. At pH 7.0, Nimesulide could not dissolve without tween and at pH 6.8, it dissolved with 1% tween. In the case of pH 6.4, 6.0 and 4.5, Nimesulide gave slight yellow tint and solubility was not completely established.

It was concluded from the above study that Nimesulide coluld dissolve visually without any aid in pH 7.4 (Tubić et al., 2013) with λ max of 393 (Petralito et al., 2012). Nimesulide visual solubility was higher in basic enviroments than acidic, this is due to their pKa value (6.4), indicating the acidic nature of the drug (SINGLA et al., 2000). Also, it was obvoius that the surfactant addition had increased the solubility of Nimesulide due to miceller solubilization that decreases the surface tension between the drug and the media and that as the concentration of Tween increases so does the solubility (da Fonseca et al., 2009). Therefore, the calibration curves were obtained at (pH 7.4 without and with 0.5% Tween), at (pH 7.0 with 0.5% Tween) and at (pH 6.8 with 1% Tween).

a. Calibration Curves

For the calibration curve obtained in phosphate buffer (pH 7.4 with 0.5% Tween-80) as seen in (Figure 4.1), the concentrations of the samples ranging from 5 to 30 ppm were plotted against their absorbance values and the standard curve had good linearity calculated with r^2 of 0.9996. This calibration curve was used for the dissolution of our formulations and the market products because the highest release was obtained in this media.

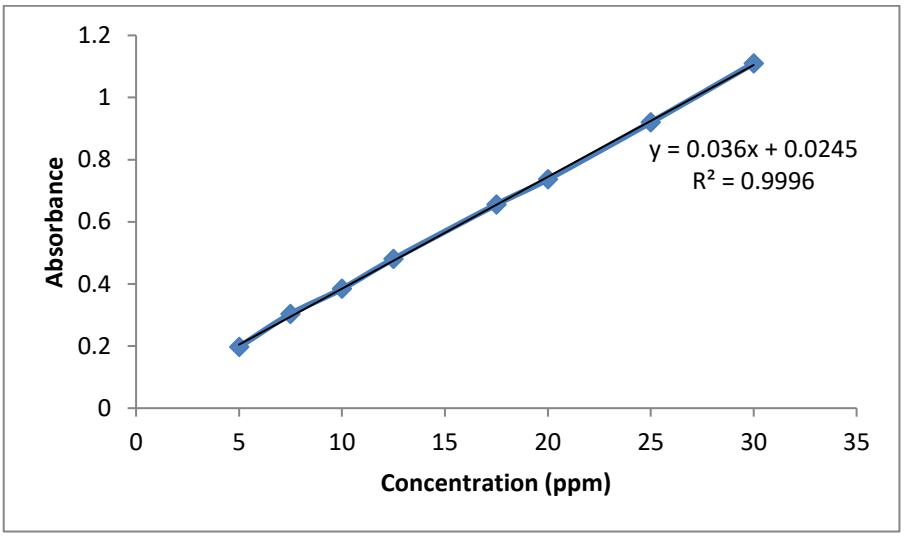

Figure 4.1: Calibration curve in (pH 7.4 with 0.5% Tween-80)

For the calibration curve obtained in (pH 7.4), the concentrations ranging from 2.5 to 25 ppm were plotted against absorbance with r^2 value of 0.9997. In (pH 7.0 with 0.5% Tween-80), the calibration curve obtained had concentrations ranging from 15 to 35 ppm were plotted against the absorbance to give an r^2 value of 0.9993. As in (pH 6.8 with 1% Tween-80), the concentrations ranging from 2.5 to 50 ppm were plotted against their absorbance to obtain an r^2 value of 0.9995.

The r^2 value in all calibration curves indicated good linearity. Also, the calibration curves in pH 7.4 and pH 6.8 with 1% Tween-80 were used in the dissolution of the marketed ND and NS products to understand the different release profile of Nimesulide in different pH medias.

b. Solubility Study

The saturated concentration was calculated using the equation from the calibration curve at pH 7.4 (y = 0.0436x - 0.0004). The absorbance value used was the value that stayed constant. This absorbance was then substituted into the equation.

The concentration obtained was multiplied by its dilution factor the (Cs) equilibrium solubility was calculated which is 0.0776 mg/ml. This value is supported by literature (da Silva, 2002).

4.2 Powder Controls

4.2.1 Particle Size Distribution

a. Light Microscope

The following (Figures 4.2- 4.5), show the different morphologies associated with Nimesulide and various excipients. It can be observed that Nimesulide appear as fine microparticles and nanoparticles. Kollidon-30, shows spherical smooth lined particles. Primojel consist of irregularly shaped ovoid or pear-shaped granules. Magnesium stearate is a very fine, precipitated or milled powder.

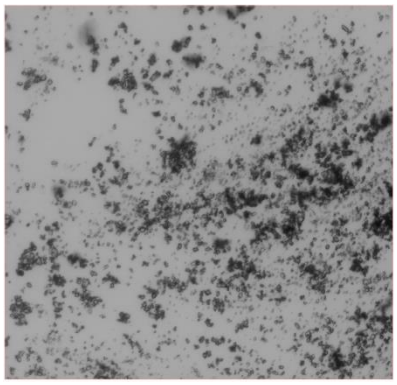

Figure 4.2: Nimesulide (x20).

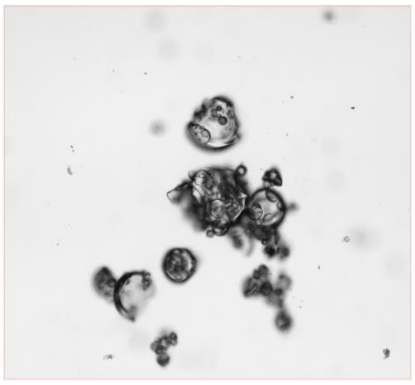

Figure 4.3: Kollidon-30 (x20).

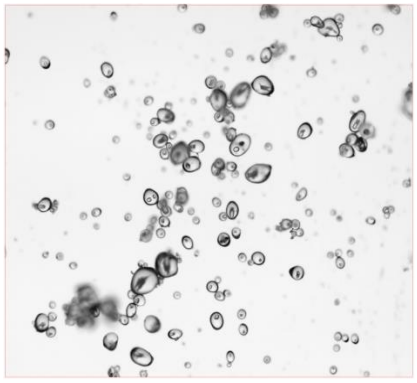

Figure 4.4: Primojel®30 (x20).

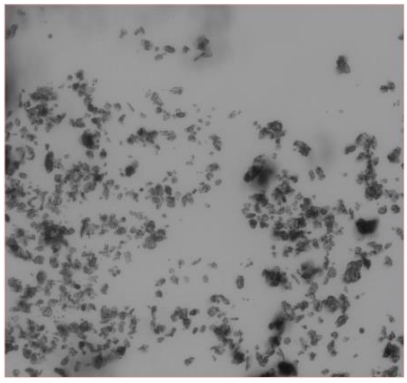

Figure 4.5: Magnesium stearate (x20).

b. Laser Diffraction

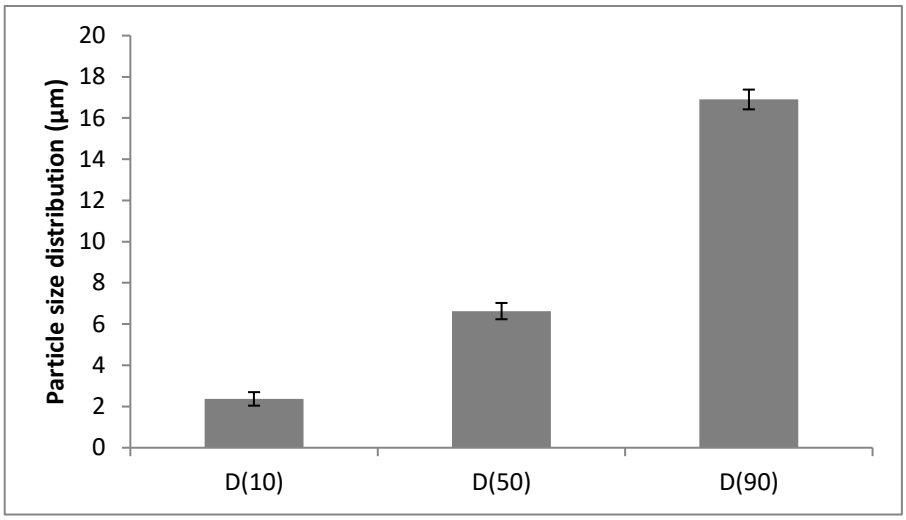

Figure 4.6: Particle size distribution of Nimesulide, (n=4)

4.2.2 Melting point of Nimesulide:

The melting point of Nimesulide showed 148.8 ºC, which is supported by the literature data (Piel, et al., 1997)**.**

4.2.3 IR-Spectrum:

As demonstrated in (Figure 4.7), observing the spectra of pure drug and our API, major absorption band at 3283 cm-1, which indicates the peak of Nimesulide drug.

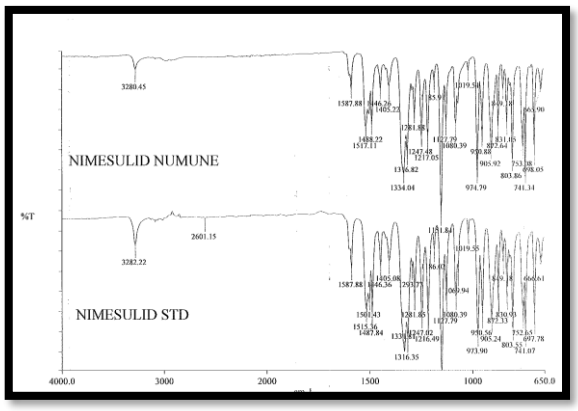

Figure 4.7: IR-spectra of Nimesulide

4.2.4 Brunauer-Emmett-Teller analysis (BET):

The surface area obtained from the BET analysis showed that the formulation that contained binder had higher surface area, meaning that the particle size is smaller than the formulation without binder. This decrease in particle size promoted more bonding between the particles in the formulation; therefore, increasing the tensile strength as seen in previous studies that with the presence of binder an increase in the tensile strength and a decrease in yield pressure, therefore this indicates that the tablets had plastic deformation and they were compressible (Abidin et al., 2011).

4.2.5 Powder Densities

From (Table 4.2), it is evident that Flowlac®100 and Kollidon®30 are considered flowable since they are known to be as directly compressible excipients used in direct compression method. Moreover, as all used APIs, Nimesulide has problems and considered to be poorly flowable.

Table 4.2: Powder properties.

Excipients	Compressibility Index	Hausner's Ratio	Flow character
Flowlac®100	20.8	1.26	Passable
Avicel®102	28.6	1.4	Poor
Kollidon®30	18.5	1.22	Fair
Nimesulide	34.2	1.52	Poor

The true density values for the formulations containing no binder and 5% binder were obtained from Yildiz Technical University and were used to plot Heckel plots and the Yield pressure (Py) values using the compaction simulator.

As observed from (Table 4.3), that yield pressure is considered to be force dependent since as the force increases from 5 KN to 10 KN either with or without binder, so does an increase in yield pressure (Roberts & Rowe, 1985). Also the presence of binder regardless the force applied decreased the yield pressure (Abidin et al., 2011), meaning that in the presence of binder, the yield pressure is force independent.

Moreover, the Yield pressure value limits according to Roberts and Rowe were, as Py value is >80 as seen at 10 KN force with and without binders, the material is considered to have brittle deformation as mentioned by (Patel et al., 2010), if Py values are within 98-1139 then it becomes compaction pressure dependent. On the other hand, as the Py value is < 80, as seen at 5 KN force either with or without binder, and then the material is considered to have plastic deformation (Hooper et al., 2016).

Table 4.3: Heckel analysis.

Formula Name	Max Mean Pressure (Mpa)	Yield pressure Py (Mpa)	R^2
K00a	53.6	73.7	0.997
K00b	101.1	93.7	0.999
K50a	53.2	68.4	0.998
K50b	83.3	83.3	0.999

4.3 Tablet Quality Controls

Table 4.4: Physical Quality controls of marketed products

Market product	ND	NS
Tablet Weight (mg)	409 ±5%	400 ±5%
Hardness (N)	60	86
Tablet Thickness (mm)	4.5	4
Friability	<1	<1

Mainly, the aim behind using the marketed products was to use the most similar product to our formulations and use it as a reference. Both market products passed their quality control tests according to EP. For instance, the weight variation test had their weights in the limit of ±5% and the friability being less than 1%.

Table 4.5: Physical Formulation Quality Controls at 5KN

Formulation	Average weight ± SD (n=10)	Hardness (N) (n=3)	Thickness (mm) (n=3)	Friability (%)
K00	404 ±0.08	33 ±0.21	3.41 ±0.01	3
K0P2	412 ±0.675	24 ±0.58	3.5 ±0.01	-
K0P5	424 ±0.843	26 ±2.08	3.59 ±0.04	5
K0K2	412 ±0.707	29 ±2.08	3.51 ±0.01	-
K0K5	424 ±0.699	28 ±1.15	3.68 ±0.01	3.3
K20	412 ±0.949	34 ±2.00	3.5 ±0.01	2.5
K2P2	420 ±0.527	32 ±2.31	3.53 ±0.02	-
K2P5	432 ±0.471	28 ±3.00	3.6 ±0.01	3.53
K2K2	420 ±0.67	26 ±2.12	3.55 ±0.01	-
K2K5	432 ±0.738	24 ±0.71	3.81 ±0.04	3.34
K50	424 ±0.966	35 ±5.66	3.65 ±0.02	2.45
K5P2	432 ±0.919	30 ±0.71	3.68 ±0.02	-
K5P5	444 ±0.568	31 ±0.00	3.8 ±0.01	4.2
K5K2	432 ±0.876	29 ±1.41	3.69 ±0.06	-
K5K5	444 ±0.422	35 ±0.00	3.94 ±0.00	2.79

First K is Kollidon®30, second K is Kollidon®CL, P is Primojel

Table 4.6: Physical Formulation Quality Controls at 10 KN

Formulation	Weight variation(%) (n=10)	Hardness (N) (n=3)	Thickness (mm) (n=3)	Friability (%) (n=10)
K00	404 ±0.02	84 ±0.31	3.16 ±0.01	0.98
K0P2	412 ±0.92	73 ±3.79	3.17 ±0.02	1.15
KOP5	424 ±1.14	79 ±3.00	3.32 ±0.07	1.14
K0K2	412 ±0.48	71 ±3.79	3.26 ±0.02	0.97
K0K5	424 ±0.52	70 ±3.21	3.38 ±0.03	0.94
K20	412 ±0.67	89 ±2.00	3.18 ±0.03	0.8
K2P2	420 ±0.67	79 ±7.81	3.29 ±0.03	0.99
K2P5	432 ±0.52	75 ±3.06	3.34 ±0.03	0.99
K2K2	420 ±0.67	82 ±3.06	3.33 ±0.03	0.9
K2K5	432 ±0.74	82 ±1.53	3.22 ±0.01	0.94
K50	424 ±0.97	90 ±3.21	3.3 ±0.03	0.73
K5P2	432 ±0.92	79 ±0.71	3.38 ±0.02	0.78
K5P5	444 ±0.57	88 ±3.54	3.43 ±0.01	0.76
K5K2	432 ±0.88	82 ±5.13	3.46 ±0.04	0.89
K5K5	444 ±0.42	90 ±10.02	3.58 ±0.01	0.8

First K is Kollidon®30, second K is Kollidon®CL, P is Primojel

From (Table 4.5 & 4.6), the physical properties of the tablets are observed at both 5& 10KN. All tablets at 5 & 10 KN passed the weight variation test as being within the acceptable range of ± 5%.

In order to compare the tablet formulations strength, the tablet weight should be fixed, and in our current research, the tablets had variable weights. Therefore in order to compare their hardness, the tablet weight should be fixed. As a result, tensile strength was calculated and used instead of the hardness value, which supports the literature as the tensile strength depend mainly on the tablet's thickness and diameter which indicates the strength in directions. As a result, tensile strength describes more accurately the strength of the tablet more than hardness (Jarosz et al., 1982).

Binder concentration and Force effect on Hardness:

From (Table 4.5 & 4.6), it can be observed that as the binder concentration increases, the hardness of the tablets increases and the tensile strength calculated increases as well (Okoye et.,al 2009). Also, as the force increases from 5 to 10 KN, the tensile strength increases as well. This can be explained by the fact that at higher forces, denser tablets are produced in which denser materials tend to have higher strength (Shang et al, 2013).

Force and Binder concentration effect on the Friability:

From (Table 4.5 & 4.6), it can be observed that as the force increases from 5 to 10 KN the tablets become less friable.

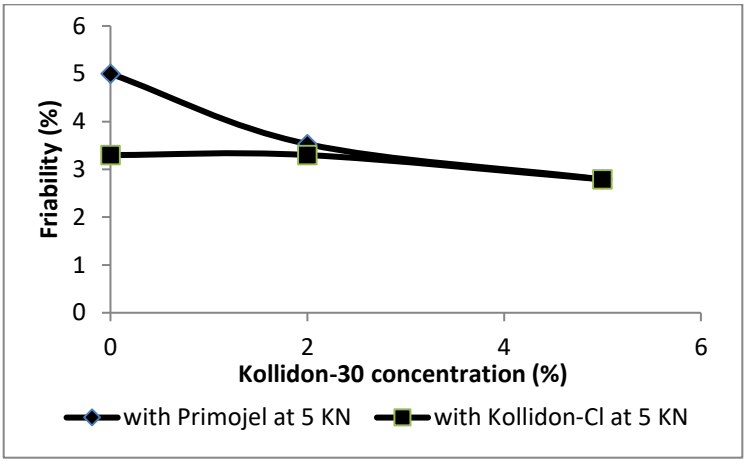

Figure 4.8: Effect of binder concentration with 5% superdisintegrants on friability at 5 KN (n=10)

It can be illustrated from (Figure 4.8), that as Kollidon-30 concentration increases, the tablets will become less friable which can be explained and correlated to higher tensile strength . Primojel showed higher friability in the absence of binder, which again can be correlated that Primojel has less deformation and therefore less bonding area, so lower tensile strength and hence more friable (Adane, 2007). On the other hand, as Kollidon-30 concentration increased, the friability became lower (Mattsson et al., 2001) with the highest decrease found in Primojel at 5KN between (0-2%) Kollidon-30.

Table 4.7: Disintegration and Dissolution Formulation Quality Controls.

Formulation	Disintegration time (sec) (n=3)	% Release in (pH 7.4+0.5% Tween-80) at 30 minutes (n=3)	% Release in (pH 7.4+0.5% Tween-80) at 60 minutes (n=3)
ND	71.2 ±1.30	79.7 ±1.04	94.1±14.35
NS	40 ±1.01	86.1 ±1.39	92 ±0.17
K00a	18 ±2.23	61.5 ±3.65	66.3 ±1.55
K00b	20 ±2.50	56.4 ±0.26	64.4 ±1.12
K0P2a	38 ±5.51	-	-
K0P2b	24 ±3.61	-	-
KOP5a	29 ±3.00	70 ±0.17	74.3 ±0.86
KOP5b	31 ±3.79	67.5 ±1.30	71.1 ±0.77
K0K2a	29 ±2.65	-	-
K0K2b	17 ±5.69	-	-
K0K5a	20 ±4.36	65.2 ±2.35	69.2 ±1.29
K0K5b	18 ±1.00	67.5 ±1.83	72.6 ±2.15
K20a	23 ±3.00	52.1 ±3.13	54.8 ±1.98
K20b	25 ±1.53	56.5 ±0.26	69.6 ±1.20
K2P2a	33 ±1.53	-	-
K2P2b	25 ±3.00	-	-
K2P5a	36 ±5.13	61.3 ±1.74	63.4 ±0.86
K2P5b	32 ±2.52	63.5 ±1.56	69.6 ±1.55
K2K2a	35 ±5.00	-	-
K2K2b	18 ±2.08	-	-
K2K5a	40 ±3.00	81.6 ±2.78	85.9 ±4.98
K2K5b	22 ±2.89	63.7 ±5.13	66.7 ±3.18
K50a	63 ±22.65	60 ±0.70	65.1 ±3.44
K50b	38 ±4.73	54.2 ±0.09	61.6 ±1.37
K5P2a	49 ±3.21	-	-
K5P2b	36 ±5.29	-	-
K5P5a	58 ±3.79	79.2 ±5.13	84.6 ±4.38
K5P5b	55 ±12.10	55.6 ±2.52	62.3 ±1.46

a=5Kn, b=10 KN, first K is Kollidon®30, second K is Kollidon®CL, P is Primojel

Generally, (Table 4.7) illustrates that, NS shows faster disintegration time when compared to ND and that both ND, NS and our formulations have their disintegration time in the required limits according to EP, all being all less than 15 minutes.

It was observed that both ND & NS products had higher % release at 75 rpm in (pH 7.4 with 0.5% Tween-80). This is because the drug is poorly soluble so with higher rpm, the thickness of the diffusion layer around each drug particle will decrease and therefore the dissolution will be enhanced (Shahrin, 2013). Moreover, the highest solubility of the drug in more basic conditions contributes to the higher release at 7.4 pH compared to 6.8 pH. Also, at 0.5% Tween-80, higher release was noted due to surfactant addition for solubility enhancement. As a result, the dissolution medium chosen for our formulations was (pH 7.4 in 0.5% Tween-80) at 75 rpm.

From (Table 4.7), it can be seen that our formulations did not pass the immediate release criteria, that the % release should be ≥ 85% released in 30 minutes, unlike the marketed products. This could be related that the sink conditions was not established during the dissolution process. This could be due to several reasons including, the amount of Tween-80 concentration was not enough to provide sink conditions and that the market products manufacture process was wet granulation instead of direct compression, which enhances the dissolution process for poorly soluble drugs.

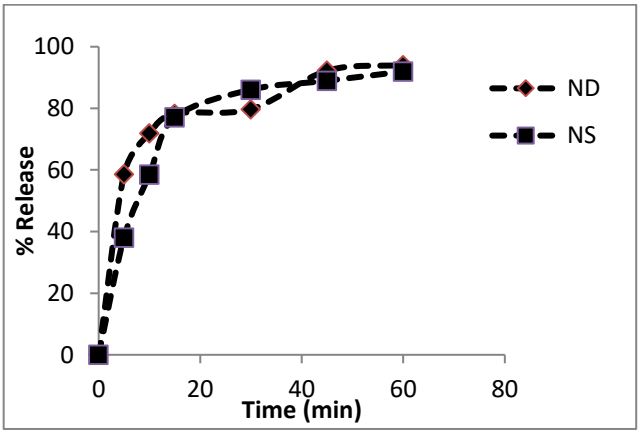

Figure 4.9: ND &NS in (pH 7.4+0.5% Tween-80) at 75 rpm

(Figure 4.9) illustrates the release profile of ND & NS and in (pH 7.4+0.5% Tween-80) at 75 rpm. The similarity (f2) value between NS & NS is 68%.

Binder concentration effect on Disintegration time:

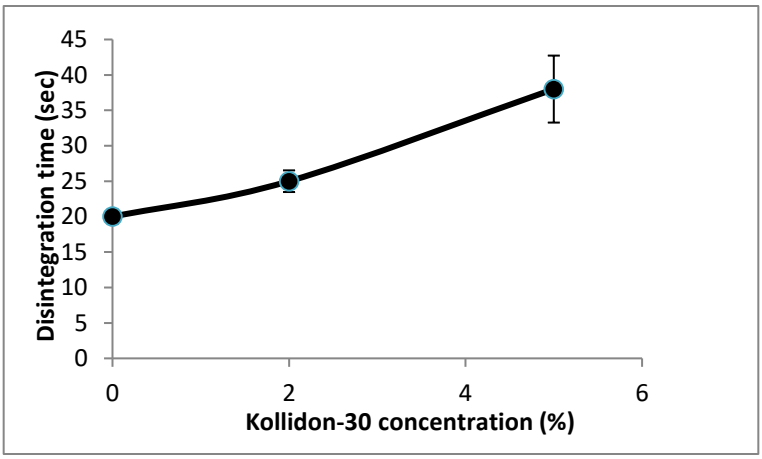

Figure 4.10: Binder concentration effect on the disintegration time at 10KN (n=3)

From (Figure 4.10), it shows that as the binder concentration increases the disintegration time increases meaning that the binder has an effect on disintegration time which was supported by literature (Okoye et al., 2009).

Effect of Superdisintegrant (SD) concentration and type on Disintegration time:

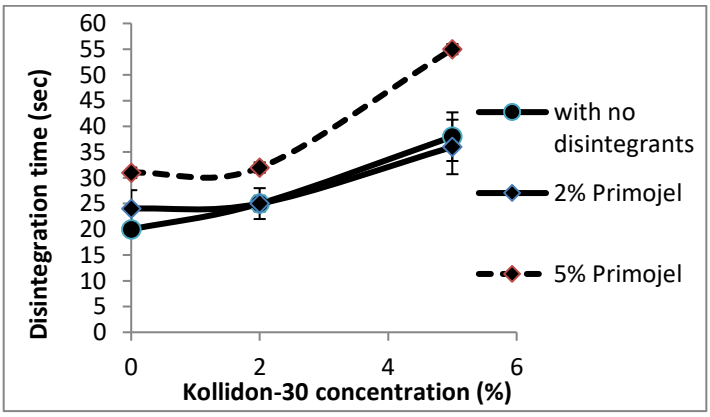

Figure 4.11: Effect of Primojel concentration on disintegration time at different binder concentrations at 10KN (n=3)

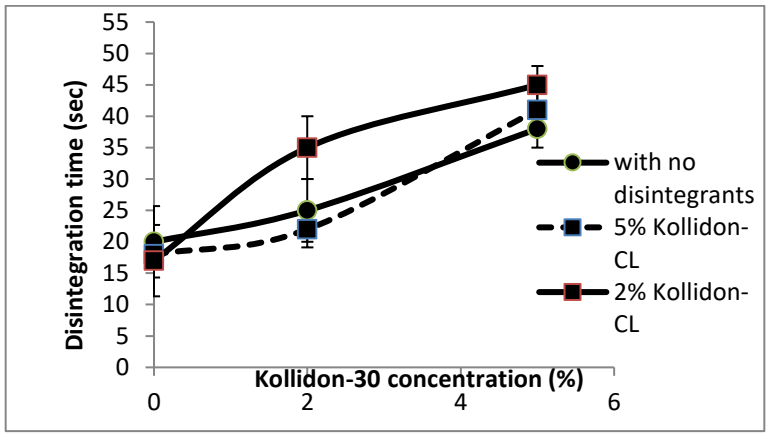

Figure 4.12: Effect of Kollidon-Cl concentration on disintegration time at different binder concentrations at 10KN (n=3)

It can be observed from (Figure 4.11 & 4.12) that with no binder, Primojel have higher disintegration time than Kollidon-CL and the higher the concentration of the superdisintegrant the longer the disintegration time, while Kollidon-CL are approximately the same. As Kollidon-30 increases in concentration, the disintegration time remains the highest for Primojel compared to Kollidon-CL and that higher concentrations of Primojel still gave more disintegration time but this was the opposite for Kollidon-CL at higher binder concentrations.

Primojel having higher disintegration time than Kollidon-CL can be correlated to higher tensile strength. Also, the higher concentration of the superdisintegrant giving longer disintegration time is obvious with Primojel since it's a characteristic of Primojel being affected by its concentration as stated by literature, that higher concentrations of Primojel will lead to longer disintegration periods (Di Martino et al., 2005). Moreover, the fact that Kollidon-Cl disintegration time is not affected by the increase in its concentration can be correlated to the fact that Kollidon-CL is mainly affected by compression force not by its concentration (Di Martino et al., 2005).

The formulations with good frialbility (<1%), were chosen to describe their dissolution profiles.

Binder concentration effect on the % Release:

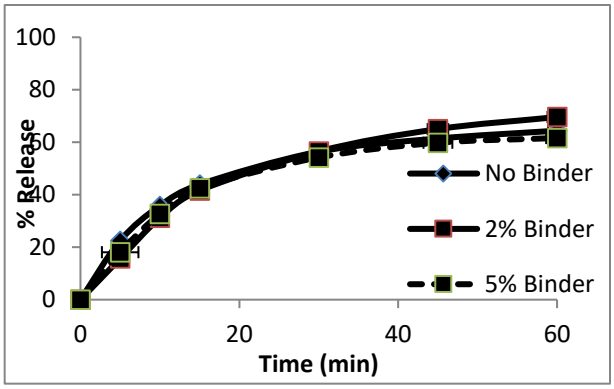

Figure 4.13: Binder concentration effect on % Release at 10 KN (n=3)

As seen from (Figure 4.13), as the binder concentration increases, the % of drug release increases. This can be correlated that Kollidon-30 at higher concentrations have dissolution enhancing effect as stated through previous findings (Rowe et al., 2009).

Superdisintegrant concentration effect on the % Release:

1. With no binder (Kollidon-30)

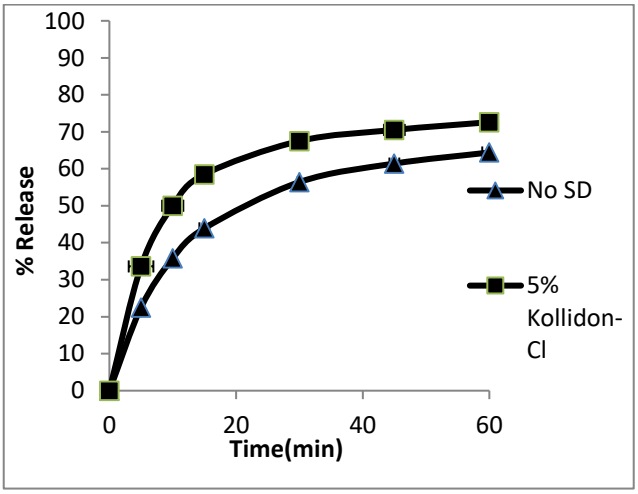

Figure 4.14: Kollidon-Cl concentration with no binder effect on % Release at 10 KN (n=3)

In (Figure 4.14), the % release showed an increase with the presence of 5% Kollidon-Cl. This is due to the faster disintegration time established and therefore better release obtained.

2. With 2% binder (Kollidon-30)

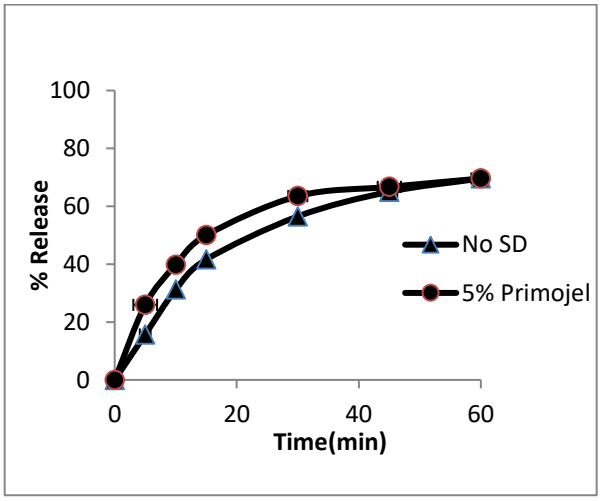

Figure 4.15: Primojel concentration with 2% binder effect on % Release at 10 KN (n=3)

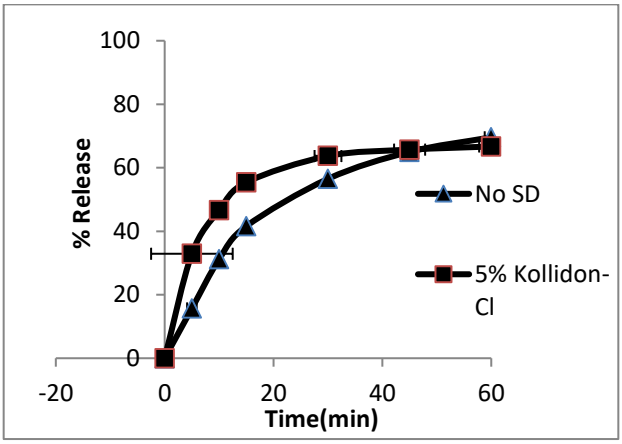

Figure 4.16: Kollidon-Cl concentration with 2% binder effect on % Release at 10 KN (n=3)

From (Figure 4.15 & 4.16), the increase in superdisintegrant concentration regardless of the type showed an increase in % release.

3. With 5% binder (Kollidon-30)

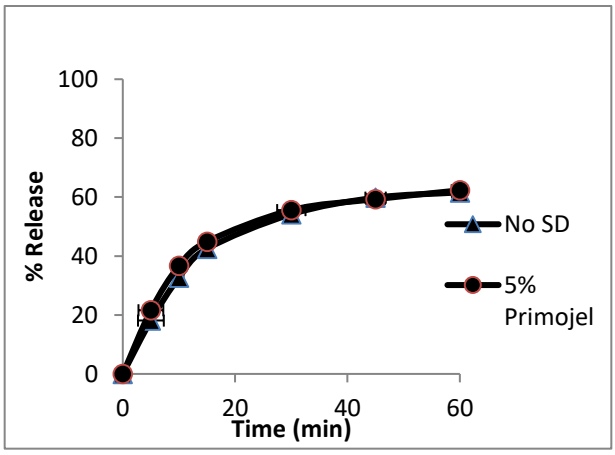

Figure 4.17: Primojel concentration with 5% binder effect on % Release at 10 KN (n=3)

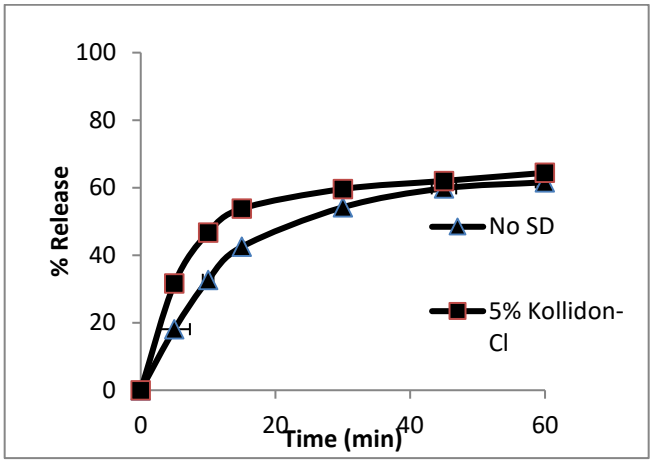

Figure 4.18: Kollidon-Cl concentration with 5% binder effect on % Release at 10 KN(n=3)

From (Figure 4.17), the presence of Primojel at 5% binder showed approximately the same % release as with the absence of superdisintegrants. While in (Figure 4.18), the presence of Kollidon-Cl at 5% binder showed higher % release than without superdisintegrants.

Regardless of the binder concentration used, the increase in SD concentration lead to increase in % release except for 5% Primojel with 5% binder, the % release was almost the same. Also, in the absence of binder, the % release obtained after 30 minutes was

higher compared to the presence of binder. This is because the tablets without binder are easier to disintegrate than tablets containing binders.

Superdisintegrant (SD) type effect at 5% concentration on the % Release:

1. With 2% binder (Kollidon-30)

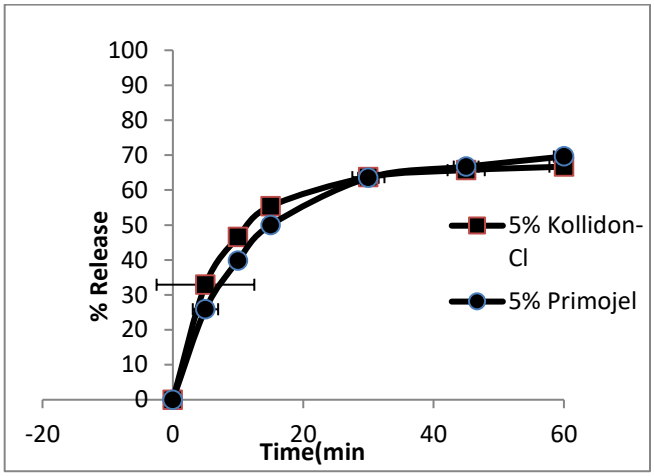

Figure 4.19: (5%) SD type with 2% binder effect on % Release at 10 KN (n=3)

2. With 5% binder (Kollidon-30)

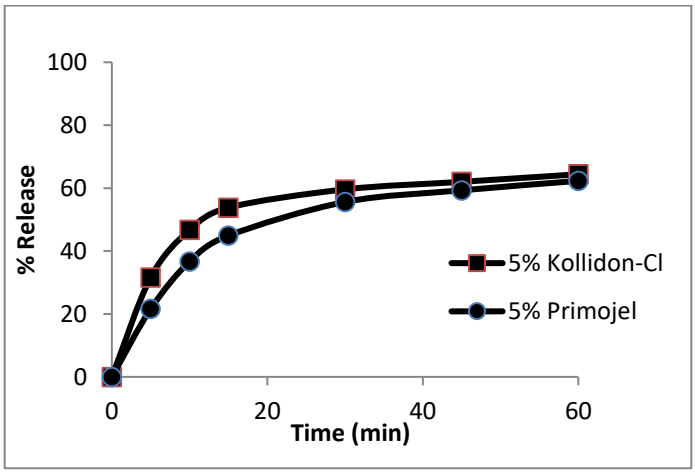

Figure 4.20: (5%) SD type with 5% binder effect on % Release at 10 KN (n=3)

In (Figure 4.19, 4.20), it compares two 5% SD with different binder concentrations % release. Regardless of the binder concentration used, Kollidon-CL showed higher % release than Primojel. Although at 2% binder, the release of both SD were almost the same at the end.

As seen from (Table 4.7), that the 100 mg nimesulid contains formulation KOK5b (It contains 225 mg Flowlac100, 75 mg Avicel 102, 20 mg KollidonCL, 4 mg Magnesium stearate) passed all physical requirements and had an (f2) similarity of 61.4 product NS as shown in (Figure 4.21). This similarity is not good as market products but acceptable.

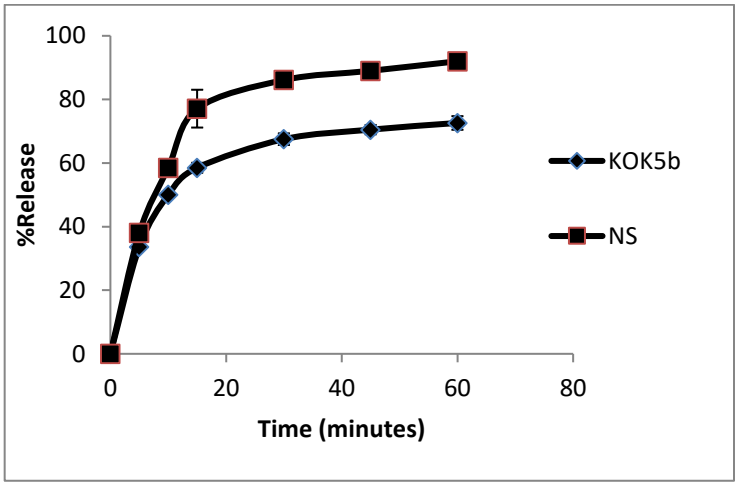

Figure 4.21: Comparing K0K5b with NS (n=3)

4.4 Quality by Design Approach

The inputs used by the Qbd MODDE software included the quality attributes which are the tablet weight, hardness, thickness, disintegration time and the percentage release at 60 minutes. A design space was obtained as seen in (Figure 4.22).

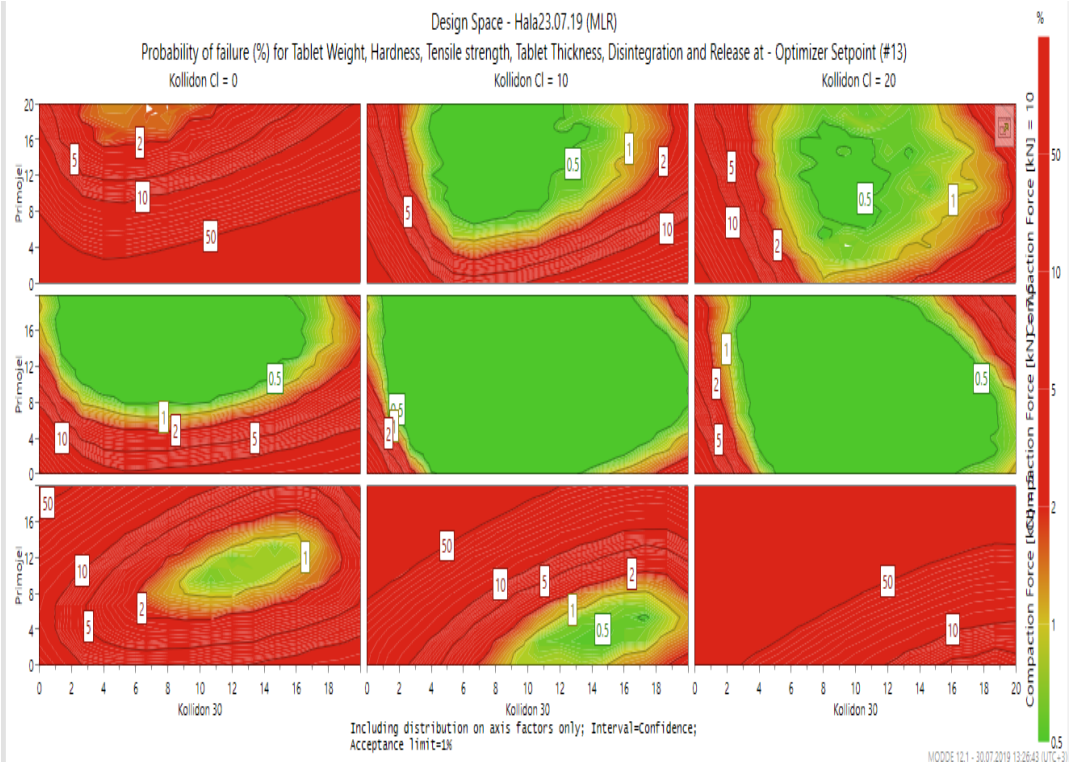

Figure 4.22: Design space of QPTT results except friability

As seen from (Figure 4.22), the compositions of the design space include Primojel, Kollidon-30, Kollidon-Cl and the compaction force applied. There are three main range zones red, yellow and green zone.

The red zone resemble the characterization range of design space which is failure percentage above 1% so formulation in this area are known to be unacceptable and do not comply with the intended specifications.

The yellow zone (acceptable range) can be determined as the right area of low confidence intervals of design space which failure percentage between 1% and 0.5%. The normal acceptable range can be determined as the right area of low confidence intervals, formulation in this area are accepted but do not comply with the intended specifications.

The green area (Operating range) have high confidence intervals and can increase the guarantee of product quality and reduction the risk of process, it has a failure percentage

lower than 0.5%. According to this design space, we take our optimal formulation from the green zone.

According to this design space which does not include friability as response, the QbD program suggested a new formulation that includes (no Kollidon-30, 20 mg Primojel, 3 mg Kollidon-Cl, 100 mg Nimesulide, 225 mg Flowlac-100, 4 mg Magnesium stearate and 75 mg Avicel-102) to be compressed at 10kN. This formulation was tested for friability as a tablet control test and the friability obtained was above 1%.

As the friability data is added to the software, the design space and the green zone will change automatically due to the fact that most friability results of the formulations were <1%, indicating that friability is an important quality attribute that should be added to give an optimum good formulation and that in further studies, the tablets friability results can be added into the software.

According to my formulation table and to my friability results that can be affected by the force show that K0K5b, had acceptable friabillity (<1%), similar dissolution profile to NS (f2=62), acceptable disintegration and hardness.

CONCLUSION

It was concluded that binders and superdisintergants had direct effects on tablet quality control tests. QbD approach formulation design used critical test results for experimental design space. Friability test should be evaluated as QTPP with hardness, disintegration, dissolution rate test together.

Compaction properties of DC powders can be determined with compaction simulator safely in terms of problem solving. In this study with QbD approach we found that friability test results of formulations were effect to the design of experiment.

To increase the solubility of Nimesulide with Tween-80, as nonionic surfactant showed positive effect but increasing the bioavailability, compositions can be prepared with different method like wet granulation technique to enhance the release rate of Nimesulide.

Further study will be continue to increase Nimesulide release rate and evaluation of CQA parameters of formulations.

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Educational Level

	Name of the Institution where he/she was graduated	**Graduation year**
Postgraduate/Specialization	-	-
Masters	Pharmacy/Pharmaceutical Technology	2019
Undergraduate	Pharmacy	2017
High school	Al-Assriya school	2012

Job Experience

Duty	**Institution**	**Duration (Year - Year)**
Pharmacy training	Al-Aqasy pharmacy	2015-2017
-	-	-
-	-	-

Foreign Languages	**Reading comprehension**	**Speaking***	**Writing***
English	Very good	Very good	Very good
French	Moderate	Moderate	Moderate

Foreign Language Examination Grade#								
YDS	ÜDS	IELTS	TOEFL IBT	TOEFL PBT	TOEFL CBT	FCE	CAE	CPE
-	-	7.0	-	-	-	-	-	-

	Math	**Equally weighted**	**Non-math**
ALES Grade	-	-	-
(Other) Grade	-	-	-

Computer Knowledge

Program	**Use proficiency**
SPSS	Very good

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