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QbD APPROACH FORMULATION DESIGN FOR METFORMIN HCl AND EVALUATIONS

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API	Active pharmaceutical ingredient
DM	Diabetes mellitus
ATP	Adenosine triphosphate
β	Beta
GDM	Gestational diabetes mellitus
Hemoglobin A1c	Glycated hemoglobin
BCS	The Biopharmaceutics Classification System
CT	Compressed tablets
DC	Direct Compression
DG	Dry Granulation
USP	The United States Pharmacopeia
MPa	Mega Pascal
QbD	Pharmaceutical Quality by Design
ICH	International Conference on Harmonisation Guidelines
QTTP	Quality Target Product Profile
CQAs	Critical Quality Attributes
CMAs	Critical Material Attributes
CPPs	Critical Process Parameters
PAT	Process Analytical Technology
FDA	The Food and Drug Administration
λ max	Lambda max
UV-VIS	Ultraviolet–visible
rpm	Revolutions per minute

QbD Approach Formulation Design for Metformin HCl and Evaluations

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SUMMARY

Aim: The aim of this study was to develop Metformin HCl 500 mg tablets via Direct Compression (DC) method by using suitable excipients and assess the formulation results. To reach the optimum formulation that can be compared to marketed product, new science-based work which is Quality by Design approach (QbD) is applied.

Material and Method: Metformin HCl is a highly soluble drug and classified as BCS class 3 group. Particular attention was applied while choosing the suitable excipients for formulations. Avicel® 102 used as a filler, three different binders, HPMC Pharmacoat®, LHPC LH-21, and Kollidon® VA 64F was used. Starch®1500 and Primojel® was used as superdisintegrant respectively . magnesium stearate is used as lubricant in this study. Tablets were pressed by using Stylcam R200 compaction simulator. After checking the compressibility of Metformin HCl itself and in combination with Avicel®102, formulations were designed with constant API:Filler ratio (1:0.75) and three different binders at varying concentrations to improve compressibility. Based on the study data, a design space was generated by umetric MOODE 12.1 software.

Findings and Results: Functional excipients versus physicochemical behavior of tablets has been investigated and it was found that, Kollidon® VA 64F has excellent results with different compaction forces on tablet tensile strength, disintegration time and friability tests. When the binder concentration increased, tablet hardness and friability results were improved and also the disintegration time was extended. All formulations quality control tests were obtained and CQAs data have been applied to the software. Design space for optimum formulation was generated and results compared with market product.

Keywords: Quality by Design, Metformin HCl, Direct compression

Metformin Hidroklorür'ün Kalite Tasarımı Yaklaşımıyla Formülasyonu ve Değerlendirmesi

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Anabilim Dalı: Farmasötik Teknoloji

ÖZET

Amaç: Bu çalışmanın amacı Metformin HCl 500 mg tabletleri doğrudan basım (DC) yöntemi ile uygun eksipiyanlar kullanarak geliştirmek ve formülasyon sonuçlarını değerlendirmektir.

Pazardaki ürünle karşılaştırılabilecek optimum formülasyona ulaşmak için yeni bilim bazlı çalışma olan Tasarımla Kalite yaklaşımı (QbD) uygulandı.

Materyal-Metod: Metfromin HCl yüksek oranda çözünür bir ilaçtır ve BCS sınıf 3 grubu olarak sınıflandırılır. Formülasyonlar için uygun eksipiyanları seçerken özellikle dikkat edildi. Dolgu maddesi olarak Avicel® 102 ve üç farklı bağlayıcı, HPMC Pharmacoat®, LHPC LH-21 ve Kollidon® VA 64F kullanılmıştır. Starch®1500 ve Primojel®, sırasıyla dağıtıcı ve süperdağıtıcı olarak kullanıldı. Bu çalışmada magnezyum stearat kaydırıcı olarak kullanılmıştır. Tabletler, Stylcam R200 compaction simulator kullanılarak basıldı. Metformin HCl'nin kendisinin ve Avicel® 102 ile kombinasyon halinde sıkıştırılabilirliğini kontrol ettikten sonra, basılabilirliği arttırmak için değişken konsantrasyonlarda sabit oranda API: dolgu maddesi (1: 0.75) ve üç farklı bağlayıcı ile formülasyonlar tasarlandı. Çalışma verilerine dayanarak, umetric MOODE 12.1 yazılımı kullanarak bir tasarım alanı oluşturulmuştur.

Bulgular-Sonuç: Fonksiyonel eksipiyanlara karşı tabletlerin fizikokimyasal davranışları ve Kollidon® VA 64Fnin farklı sıkıştırma kuvvetlerinin gerilme direnci, dağılma zamanı ve ve aşınma testleri üzerinde mükemmel sonuçlar verdiği tespit edilmiştir. Bağlayıcı konsantrasyonu arttığında, tablet sertliği ve aşınma sonuçlarının iyileştirildiği ve dağılma süresinin uzadığı tesbit edildi. Tüm formülasyonların kalite kontrol testleri yapılarak yazılıma CQA verileri uygulandı. Optimum formülasyon için tasarım alanı oluşturulmuş ve sonuçlar pazar ürünüyle karşılaştırılmıştır.

Anahtar Kelimeler: Kalite Tasarımı, Metformin HCl, Doğrudan Basım

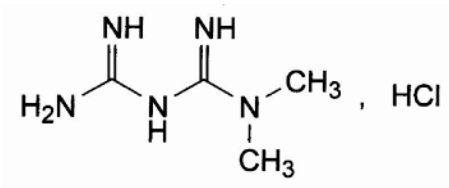
CHAPTER 1

INTRODUCTION

1.1 Metformin HCl Overview:

Metformin is available in the market in commercial forms under several brands including Glucophage®. The drug is used as first line therapy in type II diabetes, due to its efficacy and safety in controlling hemoglobin A1c, reducing weight and decreasing cardiovascular mortality rate among people affected by the disease. (Maruthur et al., 2016)

Physico-chemical proprieties:



Synonyms: 1,1- dimethylbiguanide HCl

Formula: $C_4H_{11}N_5$.HCl

Molar mass: 129.1636 g/mol

Molecular weight: 165.625 g/mol

Drug class: Antidiabetic hypoglycemic drug

BCS class: Class 3

Powder characterization: Highly crystalline, white, hygroscopic

Solubility: Highly soluble in water, > 300 mg/ml

Marketed product:

Brand: Glucophage®.

Form: immediate release oral tablet.

Doses: 500 mg, 850 mg, 1000 mg.

Brand: Glucophage XR®.

Form: extended release oral tablet.

Doses: 500 mg, 750 mg.

Polymorphism: commercially it's Form A (stable), solvent used Methanol:Water (2:1) (Childs et al., 2004)

IR Value: strong band at 3151.66 cm^{-1}

Clinical Use:

Metformin, a biguanide, is used to treat type II diabetes with a mechanism of action by reducing glucose production from the liver and increasing the sensitivity of insulin in the body. There is a little evidence to suggest benefit from metformin when taken at a dose higher than 2,000 mg daily, although the maximum permissible dose is 2550 mg (Kadoglou et al., 2010). Treatment begins at a dose of 500 mg with food and can pump up but progressively and in the form of divided doses (Katzung and Trevor).

Metformin is orally active, can bypass hepatic metabolism and excreted unaltered by the kidney. The drug is well tolerated and unescorted by side effects among most patients. This medication helped to alleviate the vascular complications associated with type II diabetes (Triggle and Ding, 2017).

There is strong evidence to suggest that metformin is associated with weight gain as compared to other drugs. On the contrary, it limits the increase in weight that may be produced when taking insulin or sulphonylurea, although events of weight gain or loss among patient populations may differ (Golay, 2008).

Despite its high clinical effectiveness, metformin is one of the most common causes of gastrointestinal disorders leading to the discomfort of patients, and developing side effects such as cramps, diarrhea, abdominal bloating, and vomiting (Bolen et al., 2007).

Healthcare providers counsel diabetic patients that they need to pay attention to drug interactions if they use them with other drugs. Metformin, for instance, reacts with anticholinergic agents that reduce gastric motility, thus increasing the presence of

metformin in the stomach and increasing its absorption in the blood, which exacerbates the side effects (May and Schindler, 2016).

Metformin lowers high blood pressure, foremost by inhibiting glucose production in the liver (gluconeogenesis). The rate of gluconeogenesis in normal person is three times lower than that of diabetic patient. Metformin, therefore, contributes to the reduction of this process by a one-third or more. (Hundal et al., 2000)

Metformin HCl has some contraindications when used in patients with:

1- Hepatic disorder diseases.
2- Metabolic acidosis in two types, acute and chronic.
3- Metformin over-sensitiveness.
4- Impairment in renal system.
5- exposure to radiological studies or treatments using iodine in the blood vessels, which may lead to renal dysfunction. (Tahrani et al., 2007).

Pharmacokinetics of Metformin

GIT absorbs 70 to 80% of metformin and the rest is excreted in the stool (Dunn and Peters, 1995). Oral bioavailability of metoformin ranges between 50 and 60 % (Dunn and Peters, 1995). The drug is absorbed in the small intestine. Food downgrades the spread of metformin and retard its absorption. Metformin's plasma protein binding is little, compared to sulfonylurea drugs which are 90% protein-bounded The maximum serum concentrations (C max) are estimated to be achieved between one and three hours for immediate release tablets , but for the extended release form of metformin needs four to eight hours (Dunn and Peters, 1995).

With a period not exceeding 24 hours, the majority of metformin absorbed through the body is filtered by the renal rout. The blood's elimination half-life is estimated of 17 hours (US FDA, 2008).

1.2 The Biopharmaceutics Classification System (BCS)

The Biopharmaceutics Classification System (BCS) is a system that is widely used in the first stages of immediate release solid oral dosage forms production, since it categorizes orally administered medications into four classes depending on the elements that control the rate and amount of absorption of drugs which are: the solubility in water, dissolution and the ability to pass from the inside of the gastrointestinal tract into the rest of the body (Felton L. A., 2013). This system enables the estimation of pharmacokinetics in a living organism of oral medication that are immediately released (Taylor and Aulton, 2013).

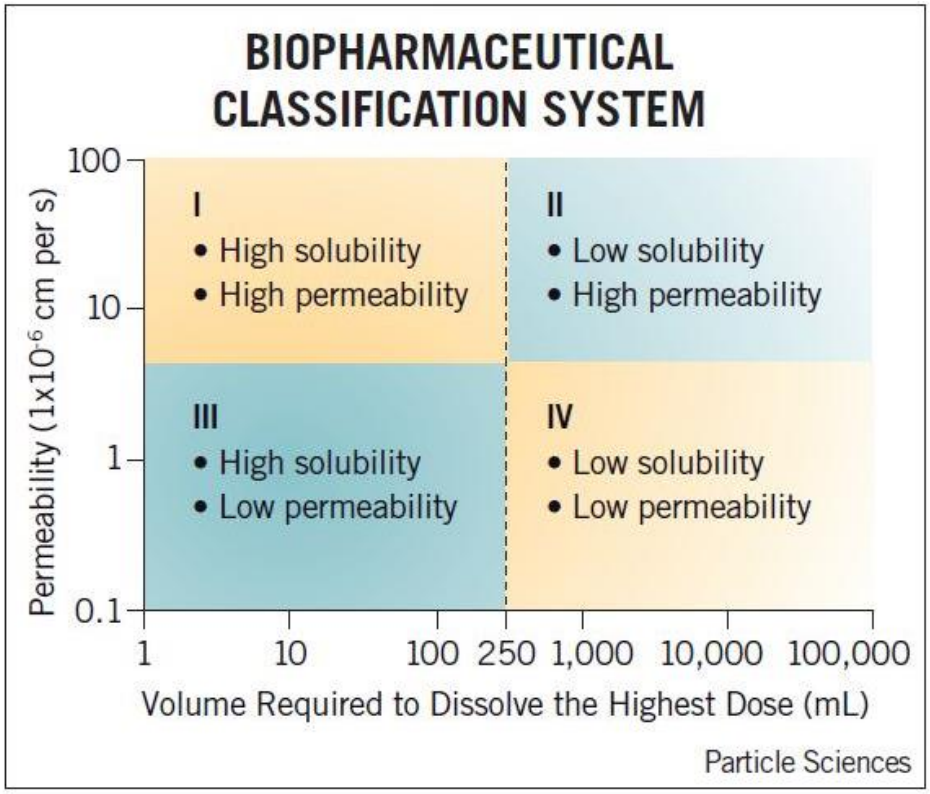


Figure 1.1 Biopharmaceutical Classification System

From: www.particlesciences.com

Class I

Medications with elevated number of absorption (a ratio of mean residence time to mean absorption time) and elevated number of dissolution (ratio of mean residence time to mean dissolution time) fit in this category, suggesting that their absorption is good, and their rate of extension is less than their rate of absorption. Dissolution of drug is the rate-controlling step of this class (Chavda et al., 2010). Known examples of them are Metoprolol, Diltiazem, Verapamil, Paracetamol and Propranolol (Chavda et al., 2010) (Khadka et al., 2014).

Class II

Medications with an elevated number of absorption and a small number of dissolution fit in this category, this means that the absorption of these medications take more time to happen since it is not as fast as medications of class I. Dissolution of drug is the rate-limiting step in this class and rate of solvation controls their bioavailability (Reddy and Karunakar, 2010). Known examples of them are Aceclofenac, Bicalutamide, Carbamazepine, Ezetimibe, Danazol, Glibenclamide, Ketoconazole, Ketoprofen, Mefenamic acid, Nifedipine, Naproxen and Phenytoin (Reddy and Karunakar, 2010) (Lindenberg et al., 2004).

Class III

Medications in this class show little permeability and elevated solubility. The rate and amount of absorption of medications in this category can vary, considering how fast dissolution happens, this variation is linked with the changing of physiology and the extent to which the membrane allows permeation. (Oyetunde et al., 2012).

The absorption rate of drugs in this category is controlled by how permeable the drug is. Class I criteria can be used if the no alterations were made on the permeation or duration of gastro-intestinal time by the formulation (Ku, 2008).

Metformin is an example of class III medications and it exhibits well aqueous solubility and little ability of passing through the cell membranes. Hence, if it was given in a solution dosage form (which is bioequivalent to an immediate release tablet which have been

dissolved entirely within 60 minutes), it will take a long time to move from the site of administration into the bloodstream and only partially (Cheng et al., 2004). Therefore, metformin's availability will not be changed by the dissolution if immediate release metformin product formulation dissolves quickly (Crison et al., 2012). Other known examples of them are Atenolol, Acyclovir, Captopril, Cimetidine, Neomycin b and Ranitidine (Yu et al., 2002).

Class IV

Medications in this class have low permeability, solubility and bioavailability. Only a small variable amount of them pass through the intestinal mucosa. Known examples of them are Bifonazole, Furosemide, Griseofulvin, Hydrochlorothiazide and Taxol (Dahan et al., 2009) (Dokoumetzidis and Macheras, 2006).

CHAPTER 2

THEORETICAL BACKGROUND

2.1 Solid Dosage Forms:

Oral route of administration is 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.

2.1.1 Tablets

Tablets are solid dosage forms taken orally containing medicinal ingredients which is intended to be released in the body in several stages starting with (Disintegration, Dissolution). Nowadays tablets are the most favorable dosage form due to their advantages over other different forms (liquids, semi-solids, and parenterals).

The mechanism of making tablets is by compressing the powder that has been previously well prepared in the lab by tablet press machines through exerting a high pressure leading to compact the particles. Normal tablets have compositions besides the active ingredients for specific functions called excipients. The powder, containing active ingredients and excipients, have went through extensive studies and calculations to assure that all contents are homogeneously mixed and interconnected. (Allen and Ansel, 2013)

Powder compression is not the only way of producing tablets, but it is the most common one because of its large-scale production benefit. Molding process is of good interest, but it’s limited because of small-scale manually operated method properties, (it could be large by tablet machinery). Producers prefer large-scale production because it is cost-effective.

Shapes of tablets are carefully considered within specific parameters to be acceptable by patients. Tablets take the forms of several shapes including round, oblong, cylindrical, oval, triangle, with the option to be scored or grooved for ease of breaking into two halves

or more for enhancing patient's ease of swallowing and ensure that the dose is accurately administered.

Tablets are characterized by several advantages such as easy packaging and shipping, chemical stability, and convenience. As any product cannot be devoid of disadvantages, the unfavorable part of producing pills is some drugs resist compression, or owing poor wetting characteristics, slow dissolution, bitter taste , moisture sensitivity, and their administration may be difficult by unconscious people or children.

2.1.1.1 Compressed Tablets (CT)

Compressed tablets (CT) are the most common form of tablets due to their ease of production and cost effectiveness. When external mechanical forces are applied to a powder mass, there is normally a reduction in its bulk volume, and by using specific tablet presses and different types of punches, tablets in its compressed form are obtained (Aulton and Ansel, 2013).

Powders are prepared by adding the appropriate excipients to the active pharmaceutical ingredients. Excipients like binders, disintegrants, and polymers play crucial role in manufacturing, using, and holding CT. After the final form of the CT is ready It can be coated in consonance to the desired purpose of its manufacture and the required characteristics (Aulton and Taylor, 2013).

2.1.1.2 Coated Tablets

Tablet coating is a process in which dry layer of special coating material is applied to a tablet containing API to get extra benefits over uncoated. Main aims for coating are controlling release profile of tablets, masking bitter taste and unpleasant appearance, protecting the drug from external pollutants, easing the swallowing of large tablets, and controlling the site of action of the drug. (Allen and Ansel, 2013)

Film Coated Tablets

Compressed tablets are covered by little layer of polymeric or water-soluble material which is normally colored. Film coating is a preferable process over other coating processes because it can be done in short time.

2.2 Functional Excipients for Tablets

Excipients is compositions added besides the active ingredients for specific functions like: (Fillers, binders, disintegrants, lubricants). These additives must contain the ideal properties for manufacturing:

1- The integrity and non-toxicity of these substances must be ensured and the appropriateness to the regulatory laws of the countries to be promoted within.
2- They must be physiologically inactive.
3- You should check that these substances do not react against each other or with the active ingredient.
4- They must be devoid of any inadmissible microbiological contents.
5- A consideration of their cost effectiveness.
6- They should have no mischievous effect on bioavailability of the drug.

2.2.1 Fillers

Fillers prepared to make up the needed bulk of the tablets when the dose is not sufficient to give the intended bulk. Most probably they are used with low doses because if the dose is too high and compressible there is no need to increase the weight. Of course, these are not the only reasons that prompted manufacturers to use fillers but to improve the cohesion of the components of the drug and increase its flow, in addition to raise the ability to use direct compression technology. Examples on diluents include (starch, lactose, diabasic calcium phosphate, cellulose (MCC, Avicel)) (Felton L. A., 2013). Also microcrystalline cellulose MCC (Avicel® 102) used as tablet filler in concentrations of (20-90)% (Rowe et al., 2009).

2.2.2 Binders

Binders are materials that hold the components unitedly in the tablets and they can be combined in either dry or liquid form while achieving granulation process to compose granules or to aid cohesion compacts to ease direct compression mechanism (Aulton and Taylor, 2013).

Binders are categorized in consonance with their function:

1- Wet binders are deliquesced in a solvent to use in wet granulation method, examples like: (water, alcohol, gelatin, hydroxypropyl methylcellulose (HPMC)).
2- Dry binders with powder mixture, whether used for direct compression or next to wet granulation process, examples: (polyethylene glycol, cellulose, PVP, copovidon (Kollidon® VA 64 F), HPMC, Low-substituted HydroxyPropylCellulose (LHPC)).

Hydroxypropyl Methylcellulose (HPMC) is used as binder in oral tablets, and as film-coating. HPMC has several grades differing in their viscosities and functions. Moreover, low-substituted HydroxyPropylCellulose (LHPC) are used as binder and disintegrant in dry granulation and direct compression methods. It has a number of grades that differ in particle size and particle size distribution. Copovidon (Kollidon® VA 64 F) is one of the best binders in direct compression method (Rowe et al., 2009).

2.2.3 Disintegrants

Disintegrants used to ease disintegration or separation of the tablets components when they interact with water in the gastro intestinal tract in the body. It can react by evoking water intake into the tablet, bulging, and causing the tablet to crack aside. This disintegration is pivotal to the following dissolution process of the medication, and to the fulfilment of drug bioavailability. Examples on disintegrants include starch and starch derivatives, sodium carboxymethyl cellulose (Ac-Di-sol), PVP (Allen and Ansel, 2013).

Pregelatinized Starch (Starch 1500): modified starch which is used in tablet preparation in different functions, one of them as tablet disintegrant in concentrations of (5-10) %. It’s preferred over normal starch because its enhancement of flow properties and

compressibility in Direct Compression (DC) and Dry Granulation (DG) (Rowe et al., 2009).

2.2.4 Lubricants

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

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

Magnesium Stearate: broadly used in pharmaceutical industry as tablet lubricant with concentrations of (0.25-5.0) % (Rowe et al., 2009).

2.3 Pre-formulation Study

Pre-formulation 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 and 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, hygroscopicity and solid-state characteristics such as, particle size and surface area analysis. (Kesharwani et al., 2017).

2.3.1 Particle Size Characteristics

Light Microscopic Analysis

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

Laser Particle Size Analyzer (Laser Diffraction)

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

2.3.2 Powder Flowability

Carr's Compressibility Index and Hausner's Ratio used to measure the powders flowability and compressibility. The United States Pharmacopeia (USP) and National Formulary define the compressibility index as "an indirect measure of bulk density, size and shape, surface area, moisture content, and cohesiveness of materials because all of these can influence the observed compressibility index. They are determined by measuring both the bulk volume and the tapped volume of a powder" (USP, NF).

The following equations are used to calculate the compressibility index:

Compressibility index = {(Tapped density - Bulk density) / Tapped density} *100
Hausner's ratio = { Tapped density / Bulk density }.

The table 2.1 below describes the ranges and characteristics of Carr's index and Hausener's ratio.

Table 2.1 Scale of Flowability (USP, NF)

Compressibility index	**Flow character**	**Hausner's ratio**
≤10	Excellent	1.00-1.11
11-15	Good	1.12-1.18
16-20	Fair	1.19-1.25
21-25	Passable	1.26-1.34
26-31	Poor	1.35-1.45
32-37	Very poor	1.46-1.59
>38	Very, very poor	>1.60

2.4 Tablet Manufacturing Methods

The manufacturing of compressed tablet dosage forms which are prepared from powders can be done by direct compression, wet granulation or dry granulation (Allen and Ansel, 2013).

2.4.1 Direct Compression (DC)

As name of the method suggests, it involves ingredient substances that are compressed with no need to change any physical traits of any of the components (Felton L. A., Remington-essentials of pharmaceutics. , 2013). This production method consists of 2 processes: powder blending then tableting (Aulton and Taylor, 2013).

This technique of manufacturing tablets was a result of many attempts to increase the efficiency of tablet processing, to reduce total of time for production and to decrease production expenses by utilizing the minimum number of workers, facilities and working areas for each procedure (Singh, Martin's physical pharmacy and pharmaceutical sciences., 2006).

Since water and high temperatures have no role and are not used in this method, the powder blend will be more stable (Gad, Pharmaceutical manufacturing handbook: production and processes (Vol. 5)., 2008). Another advantage of tablets that are directly compressed is that their dissolution tends to take less time because the tablet disintegrates quickly into primary medication particles (Marlowe and Shangraw, 1967).

On the other hand, in this method more quality assessments are needed to be done before processing. Formulas that are directly compacted usually require custom made fillers and dry binders which are in fact highly priced compared to classical ones (Patel et al., 2011).

In general, restrictions of direct compression method are technical, for example to deal with a powder of good flowability and blk density, it is obligatory to use particles that are quite big in size which are not very easy to blend into a uniform mixture which have a high chance of segregation (Duberg and Nyström, 1986). Another example is when the entire powder mixture is mostly made up of the medication itself which happens to be not

easily compacted, this will make the tablet formation a difficult process (Nyström and Glazer, 1985).

If the drug material in a tablet was ≤ 25%, it could be directly compressed if an appropriate diluent was used in the formula which will function as a carrier for the medication. Diluents used in direct compression method must possess good flow and compressible features (Mir et al., 2010).

Direct compression is suitable for 2 types of formulations: the medications that are quite soluble that could be processed as coarse particles to guarantee an adequate level of flowability, and the medications that are quite potent where only a small number of milligrams are found in one tablet and could be combined with quite coarse excipient particles which will have a leading role in flowability and compactability of the formula (Jivraj et al., 2000) (Goto et al., 1999).

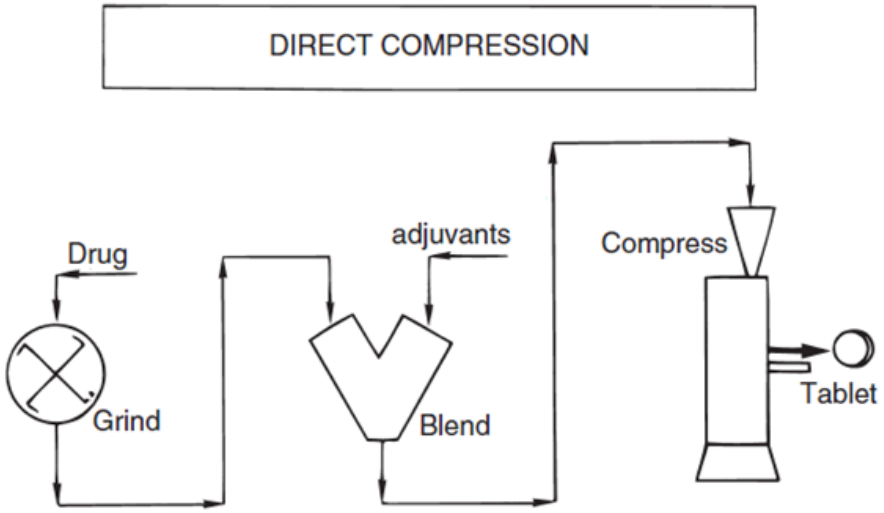


Figure 2.1: Direct Compression method for tablet preparation (Allen and Ansel, 2005)

2.4.2 Granulation Methods

Granulation is defined as the procedure in which particles agglomerate and powder components size is increased to obtain required processing characteristic (Horisawa et al., 2000). Granulation methods are used to enhance powder compaction qualities, flowability and to decrease the chance of mixture segregation because of a more uniform particle size and bulk density Granules could be made by 2 techniques, wet and dry granulation depending on how stable the active ingredient and excipients are (Arndt et al., 2018).

Dry Granulation (DG)

In this method, the active component, lubricant and in some cases a diluent are mixed together (Freitag et al., 2004). It is required that either the active component or the diluent to contain cohesive characteristics (Grote and Kleinebudde, 2018). Then, primary powder particles are aggregated by using high pressure (Gupte et al., 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 et al., 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 and Kleinebudde, 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 et al., 2008).

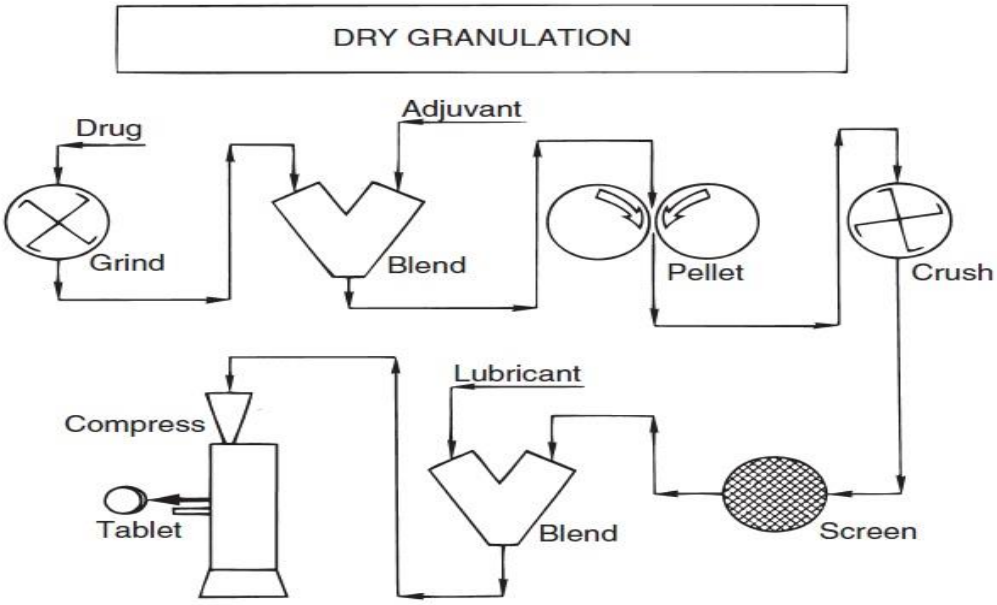


Figure 2.2: Dry Granulation method for tablet preparation (Allen and Ansel, 2005)

Wet Granulation (WG)

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 et al, 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 et al., 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 et al., 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 et al., 2001). Water is commonly chosen because it

costs less and for environmental reasons (Kiekens et al., 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 et al., 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 et al., 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 and Sakr, 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 apparatuses: low Shear mixers, high Shear mixers, fluid-Bed granulators, spray dryers, or extruders and spheronizers.

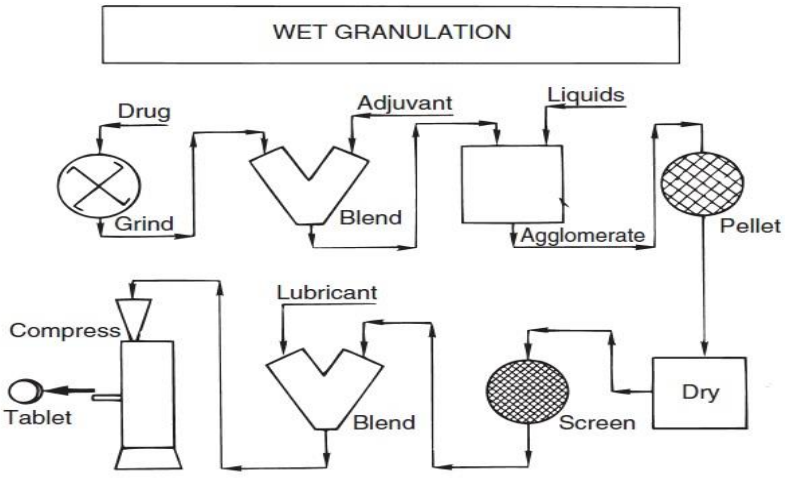


Figure 2.3: Wet Granulation method for tablet preparation (Allen and Ansel, 2005)

2.5 Quality Control Tests

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

2.5.1 Weight Variation

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

Table 2.2 Weight variation tolerance for uncoated tablets

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

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

2.5.2 Hardness

Tablets must have some toughness and resistance to fragmenting, scraping or cracking due to production process, storage environments, transference before being used to gain client approval and satisfaction. On the other hand, immediate release dosage units should easily disintegrate and dissolve after being taken by the patient (Chen et al., 2001).

Tablet hardness or crushing strength is a method to detect the level of force (expressed in Newton) required to shatter a dosage unit. Compressed tablets tent to exhibit less friability

than chewable tablets (Podczeck et al., 2015). During manufacturing of dosage units, the required forced is applied and usually the higher the pressure utilized the more solid the tablets, although tablet rigidity may be altered by formulation structure and production (KITAZAWA et al., 1975).

Another factor that determines tablet rigidity is die fill, if this factor was fixed, and more force was used, this will result in elevated firmness and reduced thickness (Hill P. M., 1976). In case the applied force was always steady by keeping a specific space between the 2 punches of the machine, firmness elevates if the die fills were elevated and reduces with less die fills (Tho and Bauer-Brandl, 2011).

Tablet hardness also depends on the volume and mixing period of the materials used in producing tablets such as lubricants and excipients. Tablets smaller in size demand less strength to be broken and for that reason are considered “softer” than bigger tablets (Nicklasson and Podczeckb, 2007).

2.5.2.1 Tensile Strength

As tensile strength calculations depend on thickness and diameter of the tablet, and indicate the strength in directions, the tensile strength describes tablet strength more accurately than hardness (Jarosz and Parrott, 1982). It expressed by (MPa) unit.

2.5.3 Friability

A method to inspect how resistant a tablet is to cracks and scratches after being compressed due to production process, transport, handling or storage conditions (Paul and Sun,2017).

Abrasions may happen as a result of tablet shape or not containing adequate moisture in its formula nor enough binder. Compressed tablets tend to exhibit less friability than chewable tablets (Gong and Sun, 2015).

2.5.4 Thickness

If pressing force was fixed, thickness of tablet will be affected by die fill, tablet weight, particle size distribution and the compression of particle mix. In case die fill was fixed, thickness will depend on differences in compression strength (Diarra et al., 2015). Any difference in thickness in a single batch of tablets or between producer's batches is unsuitable for client's approval of the medication. Invariable tablet thickness is important to ease packing procedures and to count tablets correctly since constant tablet thickness is used in filling apparatus as a counting method (Michaut et al., 2010).

Several factors determine the thickness of a tablets, these include the volume of fill allowed to go in the die cavity, the compaction features of the fill substance, and the force used during compression (Mascia et al., 2013).

2.5.5 Disintegration

When a tablet shatters into little pieces due to the entering of an aqueous liquid into the small pores of the tablet, this phenomenon is described as Disintegration. Tablet disintegration test is done to check if the dosage unit disintegrates in the range of time documented after being put in a fluid medium while maintaining the standard conditions. Disintegration test is an important step in manufacturing to guarantee similarity between different batches.

Disintegration depends on numerous production aspects, such as the particle size of active ingredient in the formula, the type and temperature of medium used, the worker's knowledge, how soluble and hygroscopic the formulation is, type of diluent, amount of disintegrate and binder their categories and used technique of incorporation, the amount of lubricants and duration of their mixing, force of compression used, the production technique especially compacting of granules and pressing strength needed in making the tablet. It has been shown that there is an association between physical features with tablet disintegration time with tablet disintegration forces decreasing if aqueous fluid penetration forces decreased, which leads to requiring a longer time to disintegrate (Narazaki et al, 2004). The lesser quantity of disintegrate in a tablet, the more time it requires to

disintegrate. On the other hand, the higher quantity of hydrophobic lubricant in a tablet, the more time it needs to disintegrate (Gupta et al., 2009). The higher the tableting pressure the longer the disintegration time will be as long as it is less than the crucial capping pressure (Harada et al., 2006.)

In case the disintegration was not acceptable, many kinds of disintegrants and superdisintegrants can be added inserted in the tablet preparation, such as starch and crosspovidone, which have a role in an aqueous solution uptake and swelling rate (Yoshita et al., 2013).

Apparatus

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

Regarding the amount of liquid medium, the top of the rising stroke the wire mesh should be kept under the surface of the liquid by ≥ 15 mm and the descending stroke should drop by ≥ 25 mm from the lowest point of vessel. The highest point of the basket-rack assembly must not be immerged at all throughout the process. The rising and falling strokes must be given the same amount of time and switching between strokes should be done smoothly and not suddenly. The movement in this apparatus is vertically along the basket-rack assembly axis. The basket-rack assembly contains six see-through tubes with one side open, each of them is 77.5 ± 2.5 mm in length and an internal diameter of 20.7 - 23 mm and a wall thickness ranging from 1.0 to 2.8 mm in addition to 2 plates that are responsible of holding the tubes vertically with each plate's diameter ranging from 88 - 92 mm and is 5 to 8.5 mm thick, and it contains 6 punctures, each of them is 22 to 26 mm in diameter, in the middle of the plate and similarly close to each other.

There is a cloth made of stainless-steel wires waved together placed at the bottom of the lower plate, and a mere square weave that has holes and a wire that has a diameter of 0.57 to 0.66 mm. The pieces of the apparatus are collected and firmly held by 3 screws that go through the 2 plates. Disks should not be used unless it was acceptable in the monograph. If stated in the individual monograph, every tube comes with a cylindrical disk, its thickness is 9.5 ± 0.15 mm and its diameter is 20.7 ± 0.15 mm. It should be built of an appropriate plastic substance. There are 5 holes at the bottom of the cylinder. On the cylindrical axis there is one of the four holes, the remaining holes are made in the center 6 ± 0.2 mm away from the axis on made-up lines vertical to the axis and parallel to each other. Disk surfaces should not be coarse.

2.5.6 Dissolution

It is defined as a test done under special restrictions to assess the needed time for a certain amount of the medication to dissolve into the water solution (Anand et al., 2011). This test is performed in to vitro to come out with an accurate expectation of how bioavailable the tablet is in vivo are and to inspect how stable the tablets will be after a brief and extended time (Gad, 2008).
Dissolution can be affected by numerous factors, such as physicochemical features which include particle size, the total area of the tablet surface, how soluble the drug is, acid dissociation constant, molecular size, formation of salt, and surface tension (Murthy and Ghebre-Sellassie, 1993).

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

If a medication has low solubility, many pharmaceutical techniques can be used, such as decreasing the mean diameter of the ingredient’s particles, inclusion complex, microemulsion and solid dispersion, to adjust and elevate dissolution rate (Seeger et al., 2015).

Dissolution also depends on manufacturing parameters of tablet production, such as temperature, blending, grinding, rotation speed, solvent, hardness and surface area (Hörter and Dressman, 2001). Experiment settings such as pH of the fluid, temperature, ionic strength, common ion effect, type of apparatus, speed of spinning, amount and components of dissolution medium and sample handling have a major rule in changing the dissolution of a dosage unit, for that reason they should apply with the stated conditions in pharmacopeias (Gohel et al., 2007).

Equipment

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

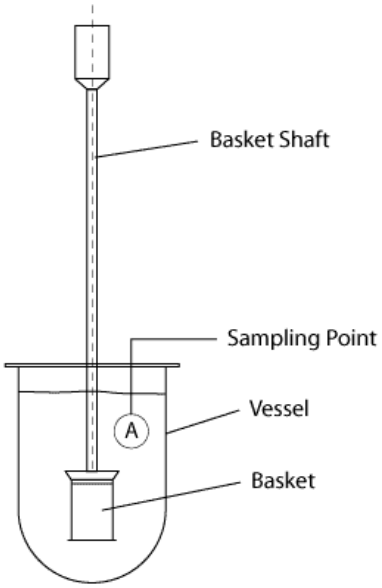


Figure 2.4 Basket Apparatus (USP)

In the rotating basket method, the tablet is put in a stainless steel basket that rotates at a fixed speed usually ranges from 50 to 100 rpm, this basket is dunked in cylindrical vessel with a convex end made of a transparent material such as glass which usually contains 0.9 L or 1 L of the medium that reached the desired temperature (37 ± 0.5 °C) in which the

tablet will dissolve. Any increase or change of the media can result in an alternation in the pH or the composition.

This apparatus also contains a motor and a metallic drive shaft. To examine the ratio of the dissolved tablet, portions of the medium are taken for evaluation at scheduled times.

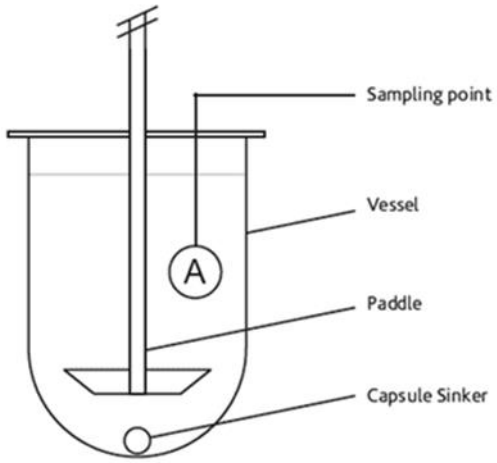


Figure 2.5 Paddle Apparatus. (USP)

In paddle method, the tablet is put on the base of the vessel, and for mixing the components a paddle rotating at a specific speed, usually at the rate of 50 to 150 rpm is used (Bocanegra et al., 1990). The blade's base and the interior of the vessel's base are kept 25 ± 2 mm apart throughout the test. To examine the ratio of the dissolved tablet, portions of the medium are taken for evaluation.

Dissolution medium

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

2.6 Quality by Design in Pharmaceutical Area (QbD)

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 et al., 2012).

QbD which is a methodical process to development of pharmaceutical dosage forms supported by International Conference on Harmonisation guidelines (ICH). It encompasses designing, developing formulations and manufacturing process to meet a set goal in the quality of the product. QbD process starts with a predesignated target (a quality target product profile QTTP) and assure product and system knowledge, depending on science and risk assessments. QbD approach emerged to strengthen the assertion of safe, efficacious drug delivery to the customers, and as a guarantee to remarkably ameliorate the drug manufacturing process, so the quality is built-in and cannot be tested (Lawrence et al., 2014).

2.6.1 Regulatory Aspects

International Conference on Harmonization Guidelines (ICH)

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

establishment of ICH Q8 , ICH Q9, and ICH Q10, each will be explained alone in this index (Aksu and Yegen, 2014).

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

Pharmaceutical Development ICH Q8 (R2)

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

Quality Risk Management ICH Q9

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

Pharmaceutical Quality System ICH Q10

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

2.6.2 Elements of QbD

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

2- Critical Quality Attribute (CQAs): Includes all properties and characteristics of the drug as an output that intended to get, physical, chemical, …etc. The expected drug products CQAs obtained QTPP and previous well information applied to drive the process development with taking in consecration to adhere with suitable limits and bounds to guarantee the required quality.

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

4- Critical Process Parameters (CPPs): Parameters that can influence the CQAs which observed prior or while process that affect manifestation, defect, and output of terminal product. In fact, the process parameters are different, some of them have higher influence on CQAs than the other, so it is important to identify CPPs with high impact over other process parameters. CPPs should be strictly controlled out of process parameters (Aksu and Mesut, 2015).

2.6.3 QbD Steps

QbD development process is illustrated in the figure.

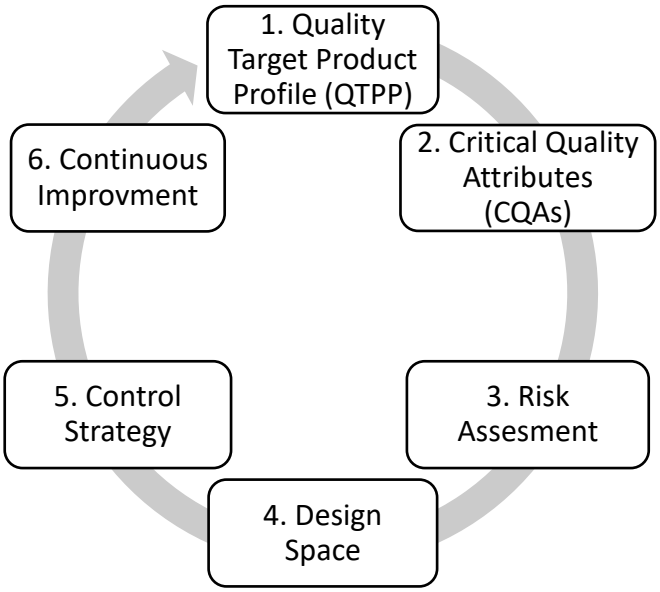


Figure 2.6: QbD Steps

2.6.4 Design Space

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

2.6.5 Control Strategy

Several rules taken from product and process understandings that assure the product's and process performance quality is achieved. In QbD methodology the control strategy demand additional realization of the process and product. It involves variables that are associated with drug substance, materials, tools, and in-process controls. Applying control strategy in QbD request additional time and expertise (Aksu and Mesut, 2015).

2.6.6 Process Analytical Technology (PAT)

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

After all, the necessity of QbD approach is highly evident nowadays because of noticeable competition between companies to deliver high quality product with cost and time saving methods. Our aim in this thesis is to apply QbD methodology in developing immediate release Metformin HCl 500 mg tablets that meets the standards of physico-chemical properties according pharmacopeia and compared to Glucophage® 500 mg marketed product.

2.7 Compaction Simulator

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

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. Metformin HCl was directly compressed using the compaction simulator (Stylecam 200R).

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

Table 2.3: Comparison of equipment for tableting studies (Çelik and Marshall, 1989).

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

CHAPTER 3

MATERIALS AND METHODS

3.1 Materials

The materials that have been used in this study are:

Metformin HCl (Sanovel İlaç San.Tic.AŞ.-Turkey) d(0.5) 33.924 µm is used, Avicel®102 (FMC, Lot#71434C) has been chosen as filler, for binder three different type binders used: Kollidon® VA 64 Fine (BASF, Lot#06212675), PHARMACOAT® HPMC (Shin-Etsu, Lot#1028064), and LHPC LH-21 (Harke Group, Lot#ZW071008), as disintegrant Starch 1500 ® (Colorcon, Lot#IN516910) has been used, Primojel® (DFE) is used as superdisintegrant and Magnesium Stearate (Peter Greven, Lot#C113930) used as lubricant.

Figure 3.1: Excipients and Chemicals Used in the Study

3.2 Methods

3.2.1 Preparation of Buffer

USP pH 6.8 Phosphate buffer is prepared by adding 250 ml of 0.2 M potassium dihydrogen phosphate to 112 ml of 0.2 M NaOH in 1000 ml volumetric flask, and volume adjusted by distilled water to 1000 ml. pH is measured by Mettler Toledo SevenEasy Benchtop pH meter. If needed adjusted with diluted NaOH.

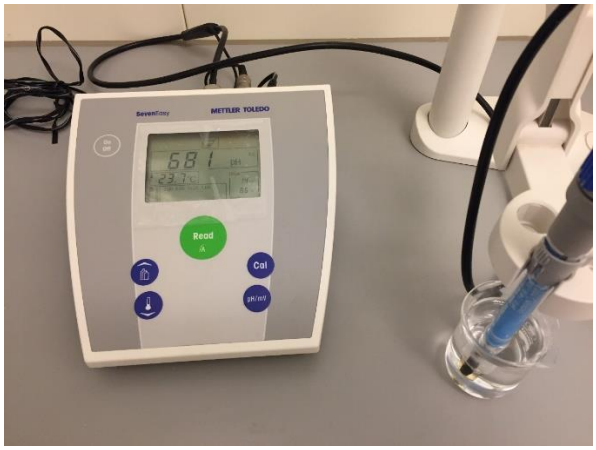


Figure 3.2: Mettler Toledo SevenEasy Benchtop pH meter

3.2.2 Calibration Curve

A stock solution of Metformin HCl is prepared by dissolving 50 mg of the drug powder in distilled water and the volume made up to 100 ml. The right dilution factors have been done from stock solution. The λ max was measured and found 233 nm, the absorbance of these dilutions was measured by Double-beam UV-VIS spectrophotometer (Shimadzu UV-1800) at wavelength 233 nm. Concentrations and absorbances for these dilutions were plotted showing a calibration curve with the equation and the coefficient of determination R^2.

3.3 Pre-formulation Study

3.3.1 Particle Size Characteristics

a- Light Microscope: The powders morphologies of Metformin HCl, Kollidon® VA 64 Fine, PHARMACOAT® HPMC, LHPC LH-21, Starch 1500, Primojel, and Magnesium stearate were tested in Yildiz Technical University-İstanbul.

b- Laser diffraction method: It was conducted from Sanovel İlaç by Malvern laser diffractometry as dry method and the particle size distribution was examined.

3.3.2 Powder Flowability

a. Bulk density:

50g of each powder was weighed and placed carefully without shaking in the measuring cylinder according to USP 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 USP, the powder was mechanically tapped by Erweka SVM (195 SVM 203) as seen in figure 3.3 and volume readings were taken until little further volume change was observed.

From both bulk and tapped densities Carr's Compressibility index and Hausner’s ratio were calculated from the equations.

Figure 3.3 ERWEKA SVM (195 SVM 203) for bulk density test.

3.3.3 IR Spectrum

Metformin HCl was analyzed by IR spectrum and the band was seen at 3151.66 cm^{-1} . The data and spectrum was provided from Sanovel İlaç company.

3.4 Metformin HCl Tablet Pre-formulation Study

To prepare formulations, particular attention should be given to all properties related to the components that are intended to be used. In this study, the aim was to develop Direct Compression Metformin HCl 500 mg tablets by using suitable excipients and assess the formulation results to reach the optimum formulation.

It's decided to use Avicel® 102 as a filler, three different binders, HPMC, L-HPC LH21 grade, Kollidon® VA 64F. As disintegrant we used Starch®1500. Primojel® has been used to see its effect as superdisintegrant. For lubrication Magnesium Stearate in constant percent.

After checking the compressibility of Metformin HCl its self which shows poor compressibility and with Avicel® 102, we decided to use 1:0.75 (API: Filler) ratio for all formulations. For each formulation gradual mixing of the excipients was applied. The specified amount of filler and Metformin HCl 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 (20kN and 30 kN). Tablets were produced with flat faced Euro B punch of 15mm diameter, using Compaction Simulator (Stylcam 200R) as seen in (Figure 3.4) and (Table 3.1a).

For HPMC we tried to use HPMC alone as binder, so we press it to check the compressibility of the powder and it was not compressible and gave no hardness value. HPMC which is a mixture of different low viscosity of HPMCs and used mainly in coating, was checked also by pressing the material alone and it was compressible, so we used it as a binder in Direct Compression for the first time to study the effect of this material.

Figure 3.4: Compaction Simulator (Stylcam 200R), MedelPharm

Table 3.1a: Composition of the Formulations in (mg), on 20 kN force.

Formulation	Metformin HCl	Avicel 102	HPMC	LHPC 21	Kollidon VA 64F	Starch 1500	Primojel	Magnesium Stearate	Total Weight (mg)
MS5P0a	500	375	0	0	0	25	0	5	905
MH2S5P0a	500	375	10	0	0	25	0	5	915
MH5S5P0a	500	375	25	0	0	25	0	5	930
ML2S5P0a	500	375	0	10	0	25	0	5	915
ML5S5P0a	500	375	0	25	0	25	0	5	930
MK2S5P0a	500	375	0	0	10	25	0	5	915
MK5S5P0a	500	375	0	0	25	25	0	5	930

Table 3.1b Composition of the Formulations in (mg), on 30 kN force.

Formulation	Metformin HCl	Avicel 102	HPMC	LHPC 21	Kollidon VA 64F	Starch 1500	Primojel	Magnesium Stearate	Total Weight (mg)
MS0P0b	500	375	0	0	0	0	0	5	880
MS5P0b	500	375	0	0	0	25	0	5	905
MH2S5P0b	500	375	10	0	0	25	0	5	915
MH5S5P0b	500	375	25	0	0	25	0	5	930
ML2S5P0b	500	375	0	10	0	25	0	5	915
ML5S5P0b	500	375	0	25	0	25	0	5	930
MK2S5P0b	500	375	0	0	10	25	0	5	915
MK5S5P0b	500	375	0	0	25	25	0	5	930
MH10S5P0b	500	375	50	0	0	25	0	5	955
ML10S5P0b	500	375	0	50	0	25	0	5	955
MK10S5P0b	500	375	0	0	50	25	0	5	955
MK10S5P2b	500	375	0	0	50	25	10	5	965
MK10S0P2b	500	375	0	0	50	0	10	5	940
MK10L5P0b	500	375	0	25	50	0	0	5	955
MK10L5P2b	500	375	0	25	50	0	10	5	965
MH15S5P0b	500	375	75	0	0	25	0	5	980
MH15S5P2b	500	375	75	0	0	25	10	5	990
MH20S5P0b	500	375	100	0	0	25	0	5	1005
MH20S5P2b	500	375	100	0	0	25	10	5	1015

3.5 Quality Controls of Formulations and Market Product

3.5.1 Weight Variation

Procedure

Ten tablets were weighed separately by Mettler Toledo AB204-S/FACT Analytical Balance. Each tablet was inspected, then weight average is calculated and compared with the weight of each sample.

According to USP the limitations for tablets that contain more than 324 mg is ± 5%, and all tablets passed the test.

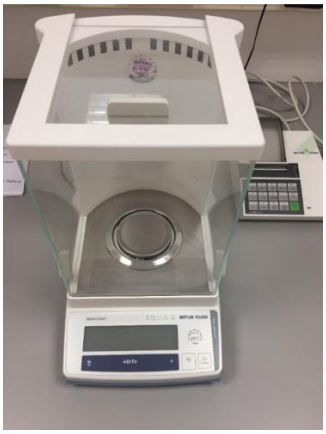


Figure 3.5: Mettler Toledo AB204-S/FACT Analytical Balance

3.5.2 Hardness

Procedure has been done using ERWEKA TBH 225 Hardness Tester:

1. The dosage unit was put between the 2 anvils of the used machine.
2. Force is applied to the tablet in order to break it.
3. The amount of power that causes the crushing of the tablet is documented.
4. **Tensile strength** is calculated by the equation :

$$\sigma_X = \frac{2F}{\pi DH}$$

Where: σX: tensile strength, F: breaking force, D: tablet diameter, H: tablet thickness.

Figure 3.6: ERWEKA TBH 225 Hardness Tester

3.5.3 Friability

Procedure is done with ERWEKA TA 220 Friability Tester:

1. Tablets are weighed then exposed to an even overturning movement in a rotating drum that has a baffle resulting in a continuous turning and dropping for a constant time, usually 100 revolutions.
2. Tablets are weighed, and the lost amount of material is documented.
3. The equation used in calculating and describing the degree of friability is:
   Percentage Friability % = X1 – X2/X1 * 100
   X1 is initial weight, X2 is final weight.

Acceptance restrictions

1. The test fails if any of the samples broke or fractured.

2. The weight reduction must not exceed 0.5% to 1% and is generally considered accepted.

Figure 3.7: ERWEKA TA 220 Friability Tester

3.5.4 Thickness

Procedure:

Separate tablets thickness can be known and documented by using a micrometer, which takes precise measurements and shows the differences between dosage units.

For tablet thickness to be accepted, the measurement can vary in a range of ±5% of the standard value.

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

Figure 3.8: Digital Caliper (TCM) for thickness and diameter

3.5.5 Disintegration

Disintegration was done by ERWEKA ZT 322 disintegration tester.

Procedure

1. One tablet was put in each of the tubes of the basket, and a disk is added.

2. The machine turned on at 29-32 cycles per minute, enabling it to rise and fall in the specified liquid medium that will be used for the immersion and keep its temperature at range of 37 ± 2 °C.

3. The disintegration time was recorded after all tablet was disappeared. Examining the dosage units, for the batch to be accepted, every single tablet should be totally disintegrated, and all particles have passed through the 10 mesh screens in the stated period of time.

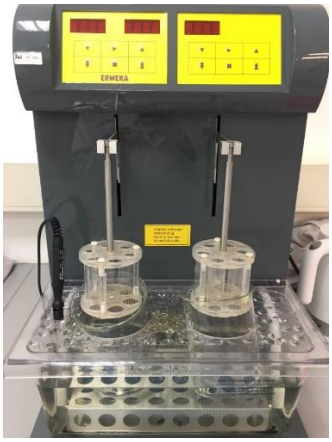


Figure 3.9 ERWEKA ZT 322 disintegration tester

3.5.6 Dissolution

Dissolution is done with ERWEKA DT 720 dissolution tester using USP Apparatus 2 Paddle type for tablets. Medium is selected according USP Metformin monograph which is pH 6.8 phosphate buffer (1000 ml), the paddle speed is done on two rpms 50, 75

Procedure:

1. Dissolution medium was inserted in the vessels.
2. The apparatus was assembled and set the medium temperature to 37 ± 0.5 °C.
3. One tablet was dropped in each vessel and set the desired rate then turned it on.
4. Samples were taken at 5, 10, 15, 30, 45, 60 minutes for analysis from the space between the blade and the face of the medium and over 1 cm away from the vessel's sides at the pre-scheduled times.
5. The vessels were closed throughout the test, while constantly checking the medium's temperature.
6. The samples were diluted with suitable dilution factor, absorbance were measured
7. by UV spectrophotometer (Shimadzu UV-1800), and the concentration were calculated from calibration curve equation. Final step was to calculate the percentage of drug release profile.

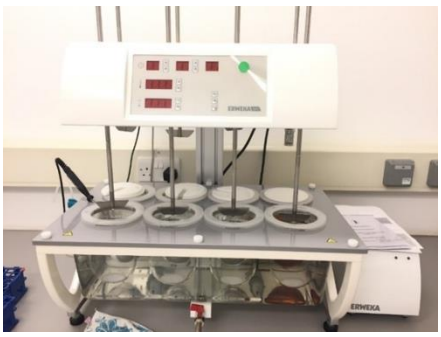


Figure 3.10 ERWEKA DT 720 Dissolution Tester Paddle Apparatus II

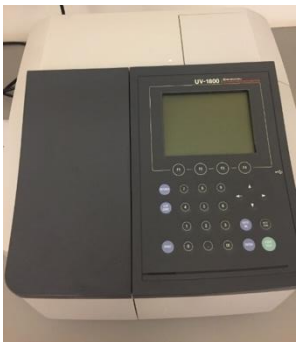


Figure 3.11 Spectrophotometer (Shimadzu UV-1800)

3.6 Quality by Design Approach

3.6.1 Target Product Profile (TPP)

Table 3.2: Target product profile of Metformin HCl.

Specification	**Target Product Profile**
Dosage Form	Immediate Release Tablet (Orally)
Dosage Strength	500 mg
Pharmacological Action	Anti-diabetic agent

3.6.2 Quality Target Product Profile (QTPP)

QTPP values in table 3.3 were defined according USP limits and market product and used these limits for the formulations.

Table 3.3: Quality target product profile of Metformin HCl.

Specification	**Quality Target Product Profile**
Weight variation	±5%
Disintegration	More than 5 minutes in distilled water
Dissolution	≥ 80% in 30 minutes
Hardness	200-270 N
Friability	< 1%

The CQAs were then determined from previous knowledge as dissolution, disintegration, tablet weight and hardness 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 Glucophage®.

3.6.3 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.

3.7 Optimum Formulation

All formulations in Table 2.3 have undergone control tests, and the results will be discussed later. After applying these results at Umetric MODDE 12.1 software to obtain design space, we got our optimum formulation and did same control tests to compare with our marketed product Glucophage® 500 mg.

CHAPTER 4

RESULTS AND DISCUSSION

4.1 Calibration curve

Concentration of samples ranging from 1.25 to 12.5 (µg/ml) were plotted against their absorbance values. The standard curve linearity was calculated with R^2 of 0.9998 as seen in figure 4.1.

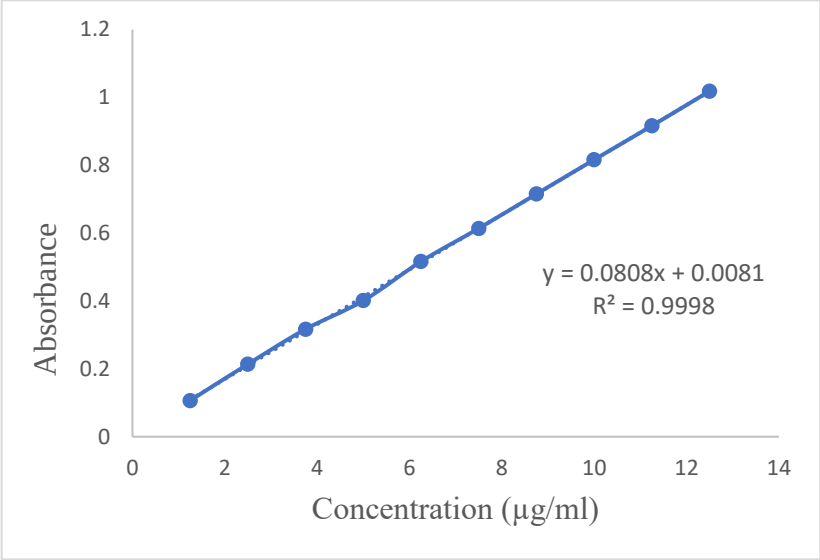


Figure 4.1: Calibration Curve of Metformin HCl in pH 6.8 Phosphate Buffer

4.2 Pre-formulation Study Results

4.2.1 Particle Size Characteristics

a) Light microscope:

The following figures (4.2, 4.3, 4.4, 4.5, 4.6, 4.7, 4.8) show the morphologies of powders used for formulations, Metformin HCl and various excipients. It can be observed in figure 4.2 that Metformin HCl appears as small cubic particles with d(0.5) of 33.924 µm. In figure 4.3 for Kollidon VA 64F, shows larger spherical structure with d(0.5) of 48 µm. In figure 4.4 HPMC particles seen as long irregular particles with average size of (50-70µm). Figure 4.5 shows L-HPC

LH 21, it is moderately fibrous particles with d(0.5) of 45µm. Starch 1500 particles which is seen in figure 4.6 has irregular appearance with d(0.5) of 24.6µm. Primojel® particles in figure 4.7 consist of irregularly shaped ovoid or pear-shaped granules, (30-100µm) in size. Magnesium stearate particles in figure 4.8 is very fine, precipitated or milled powder.

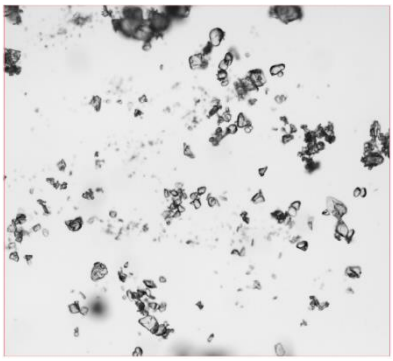


Figure 4.2: Metformin HCl (20X)

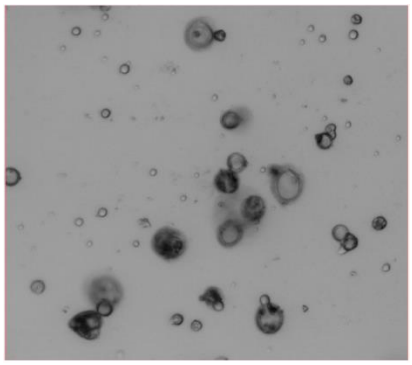


Figure 4.3: Kollidon VA 64F (20X)

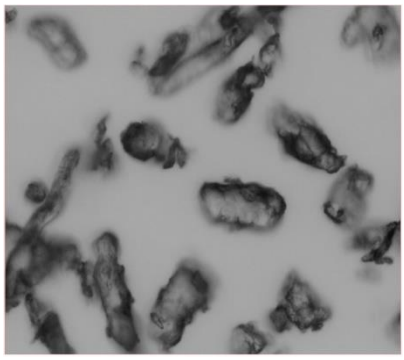


Figure 4.4: HPMC (20X)

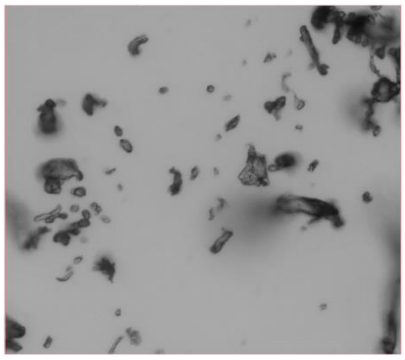


Figure 4.5: LHPC-21 (20X)

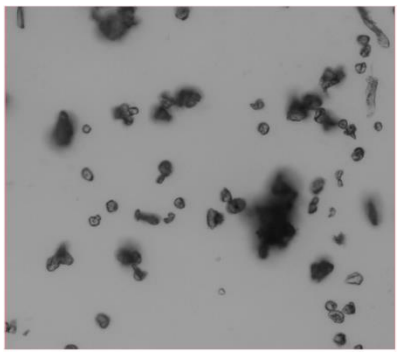


Figure 4.6: Starch 1500 (20X)

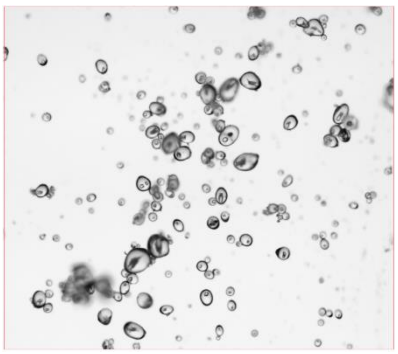


Figure 4.7: Primojel (20X)

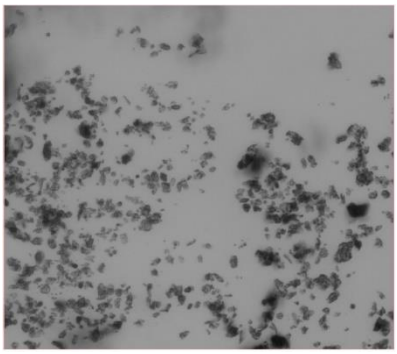


Figure 4.8: Magnesium Stearate (20X)

b) Laser diffraction results for Metformin HCl.

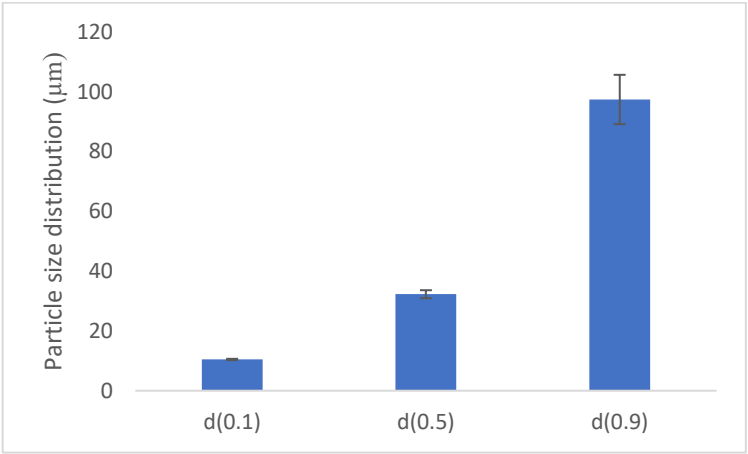


Figure 4.9: Particle size distribution of Metformin HCl (n= 6)

4.2.2 Powder Flowability Results

From Table 5.4, Metformin HCl shows very poor compressibility and flowability value. For Avicel®102 also shows close value. That's lead us to the reason that higher API:Filler ratio needed.

Table 4.1: Powder properties

Powder name	Compressibility Index	Hausner's Ratio	Flow character
Metformin HCl	43.67	1.775	Very, very poor
Avicel®102	28.8	1.405	Poor

4.2.3 IR Spectrum Analysis:

These results in Figure 4.10 obtained from supplier comparing between IR profile for standard Metformin HCl and our API. It shows that both are identical.

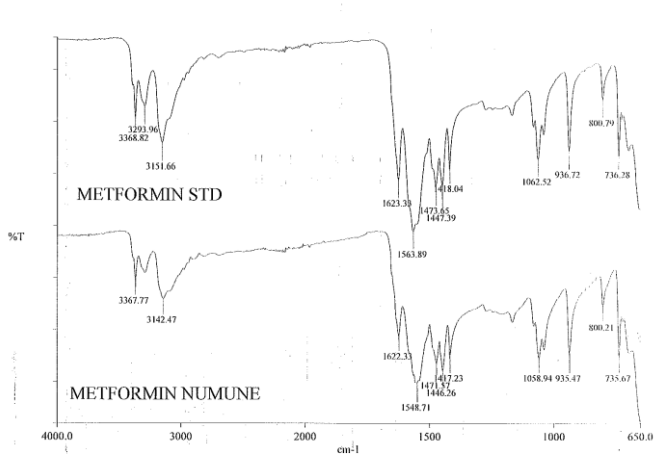


Figure 4.10 Metformin HCl IR Analysis

4.3 Quality Controls of Formulations and Market Product

Physical properties of the formulations are observed from (Table 4.2a, Table 4.2b) at both (20 and 30 kN). All formulations at (20 and 30 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 fixed, and in our current research, the tablets had variable weights. Therefore, in order to compare their hardness, the tablet weight 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).

Table 4.2a: Physical control tests results of formulations applied on **20 kN** force

Formulation	Average weight ± SD, n=10	Hardness (N) ± SD, n=3	Thickness (mm) ± SD, n=5	Diameter (mm)	Friability (%)
MS5P0a	900 ±4.43	102 ±4	4.12 ±0.24	15.1	1.30
MH2S5P0a	903.8 ±4.22	105 ±1	4.27 ±0.04	15.1	1.27
MH5S5P0a	929 ±4.09	97 ±1	4.34 ±0.02	15.1	1.63
ML2S5P0a	914.1 ±4.56	84 ±1	4.24 ±0.02	15.1	1.59
ML5S5P0a	929.7 ±4.84	116 ±2.6	4.29 ±0.02	15.1	0.88
MK2S5P0a	913.8 ±4.65	126 ±3	4.18 ±0.03	15.1	0.81
MK5S5P0a	928.7 ±4.68	129 ±2.6	4.29 ±0.01	15.1	0.83

Table 4.2b: Physical control tests results of formulations applied on **30 kN** force

Formulation	Average weight ± SD, n=10	Hardness (N) ± SD, n=3	Thickness (mm) ± SD, n=5	Diameter (mm)	Friability (%)
MS0P0b	881.5 ±4.27	88 ±1	3.87 ±0.01	15.1	1.5
MS5P0b	903.8 ±4.05	160 ±2	4.02 ±0.02	15.1	0.68
MH2S5P0b	913.4 ±4.86	174 ±1	4.09 ±0.03	15.1	0.7
MH5S5P0b	931.3 ±4.06	150.5 ±3.6	4.11 ±0.01	15.1	0.64
ML2S5P0b	913.6 ±4.92	121.5 ±1.7	4.06 ±0.02	15.1	0.96
ML5S5P0b	931.2 ±4.19	182 ± 2	4.11 ±0.01	15.1	0.66
MK2S5P0b	912.8 ±4.31	198.5 ±3.6	4.04 ±0.02	15.1	0.61
MK5S5P0b	929.2 ±4.38	192.5 ±1.7	4.1 ±0.01	15.1	0.55
MH10S5P0b	951.4 ±1.81	146.5 ±1.7	4.24 ±0.02	15.1	0.75
ML10S5P0b	955.8 ±1.77	152 ±4	4.2 ±0.04	15.1	0.58
MK10S5P0b	950.1 ±3.13	244 ±8	4.17 ±0.01	15.1	0.48
MK10L5P0b	953.1 ±1.96	313 ±1.5	4.18 ±0.01	15.1	0.55
MK10L5P2b	963.1 ±2.34	312 ±3	4.2 ±0.01	15.1	0.57
MH15S5P0b	978.8 ±2.87	178 ±4	4.3 ±0.01	15.1	0.61
MH15S5P2b	986.1 ±1.8	214 ±5	4.43 ±0.01	15.1	0.43
MH20S5P0b	999 ±2.07	207 ±4	4.45 ±0.01	15.1	0.47
MH20S5P2b	1013 ±2.49	194 ±5	4.59 ±0.01	15.1	0.56

Table 4.3a: Disintegration time results of formulations applied on **20 kN** force.

Formulation	**Disintegration time (sec.)** ±SD, (n=3)
MS5P0a	14.6 ±2.89
MH2S5P0a	17.3 ±2.52
MH5S5P0a	17.6 ±2.08
ML2S5P0a	15.0 ±1.00
ML5S5P0a	16.6 ±1.53
MK2S5P0a	19.0 ±1.00
MK5S5P0a	32.0 ±4.00

Table 4.3b: Disintegration and dissolution test results of formulations applied on **30 kN** force.

Formulation	**Disintegration time (sec)** ±SD, **(n=3)**	**% Release in pH 6.8, on 50 rpm at 30 minutes,** ±SD **(n=3)**	**% Release in pH 6.8, on 50 rpm at 60 minutes,** ±SD **(n=3)**
MS0P0b	19 ±1.00	-	-
MS5P0b	29 ±7.21	-	-
MH2S5P0b	37 ±7.02	-	-
MH5S5P0b	53 ±1.00	-	-
ML2S5P0b	23.6 ±0.58	-	-
ML5S5P0b	30.3 ±1.53	-	-
MK2S5P0b	62 ±7.21	-	-
MK5S5P0b	179 ±65.3	91.1 ±3.47	91.5 ±0.55
MH10S5P0b	137.6 ±23.1	-	-
ML10S5P0b	37.3 ±2.52	-	-
MK10S5P0b	460 ±26.5	72 ±2.84	88.5 ±0.69
MK10L5P0b	498 ±15.3	59.2 ±1.39	84.6 ±3.45
MK10L5P2b	489 ±17.6	60.7 ±2.01	79.6 ±3.59
MH15S5P0b	326 ±55.5	60.6 ±3.4	72.7 ±1.59
MH15S5P2b	355 ±56.3	58.8 ±0.42	81.4 ±3.03
MH20S5P0b	465.3 ±26.2	33.4 ±3.47	52 ±2.62
MH20S5P2b	768.3 ±56.2	41.5 ±1.04	51 ±1.45

Mainly, the aim behind using the marketed products was to use the most similar product to our formulations and use it as a reference. Table 4.4 shows weight variation, thickness, and hardness for market product Glucophage 500 mg.

Table 4.4: Weight variation, Thickness, and Hardness of Market product.

Market product	**Glucophage® 500 mg, (n=10)**
Tablet Weight (mg)	529 ±4.89
Hardness (N)	254 ±1.52
Tablet Thickness (mm)	6

4.4 Design Space of Formulation Using QbD Approach

The quality controls result for formulations were inputted into the software to train the program with our data to get the optimum formulation. It included, the tablet weight, hardness, disintegration time and dissolution. From these responses a design space was obtained.

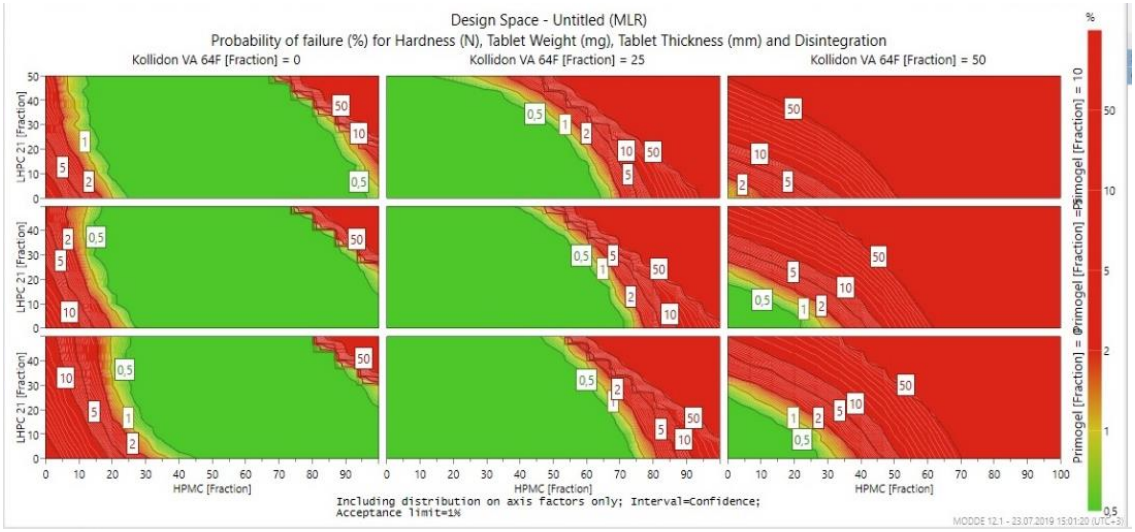


Figure 4.11 (4D) Design Space obtained by Umetric MODDE software.

As seen in Figure 4.11, there are three main range zones red, yellow and green zone.

The red zone resembles 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 optimum formulation from the green zone. The optimum formulation composition seen in table 4.5 and its physical control test seen in table 4.6.

Table 4.5 Optimum Formulation obtained by Umetric MODDE software.

	Factor	Role	Value	Graph	Factor contribution
1	HPMC	Free	54,1156		30,2061
2	LHPC 21	Free	49,7055		9,82812
3	Kollidon VA 64F	Free	19,695		38,6468
4	Primogel	Free	5,5354		8,46354
5	Starch 1500	Free	0,27093		3,57486
6	Compaction Force (kN)	Free	27,7506		9,2805

Table 4.6: Weight variation, Thickness, and Hardness of optimum formulation

Market product	**Optimum Formulation**
Tablet Weight (mg)	1009 ±3.49
Hardness (N)	212 ±2.51
Tablet Thickness (mm)	4.47 ±0.01

4.5 Composition Effect on Tablets behavior

Figure 4.12 shows the correlation between tensile strength and binder concentrations on 20kN force. As known in the literature binder concentrations have a proportional relationship with tensile strength, increasing the binder will yield harder tablet (Okoye, 2009). This is in agreement with our results obtained with using Kollidon VA 64F and LHPC 21 with exception to HPMC.

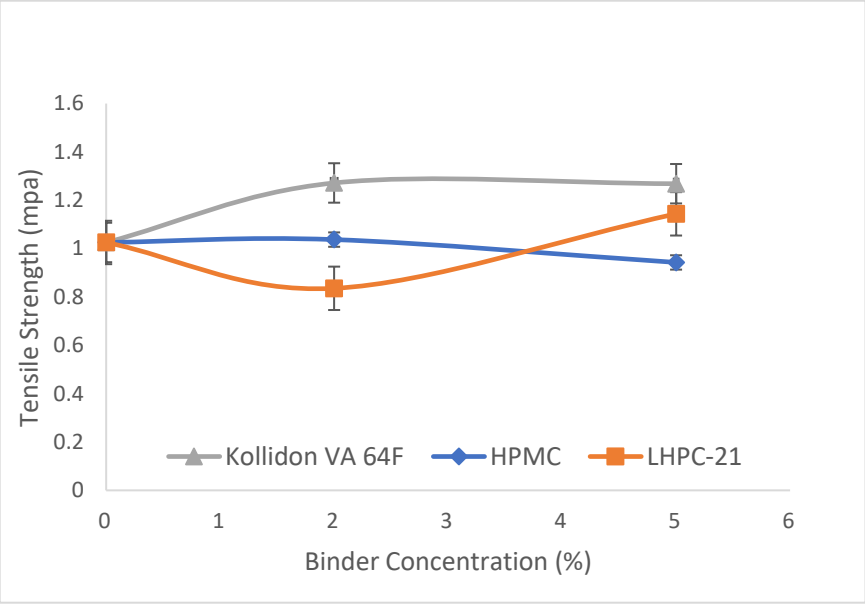


Figure 4.12 Effect of binder type and concentrations on tensile strength under 20kN force, (n=3).

When no binder in the formulation is used, the tensile strength was around 1 MPa.

The graph shows that Kollidon VA 64F reached the maximum tensile strength at 2% after that at 5% changing the concentration didn't affect the tensile strength.

Regarding LHPC-21, at 2% there was no binder effect on formulation, but for 5% it showed slightly increase in tensile strength. LHPC-21 shows higher effect at higher concentrations. Noticeably, HPMC had no binder effect on formulation.

Figure 4.13 displays the correlation between tensile strength and binder concentrations on 30 kN force. Kollidon VA 64F showed same behavior as on 20 kN for 2% and 5% in Figure 4.12. As known that povidone is the top binder that ever used (Kolter, 2000).

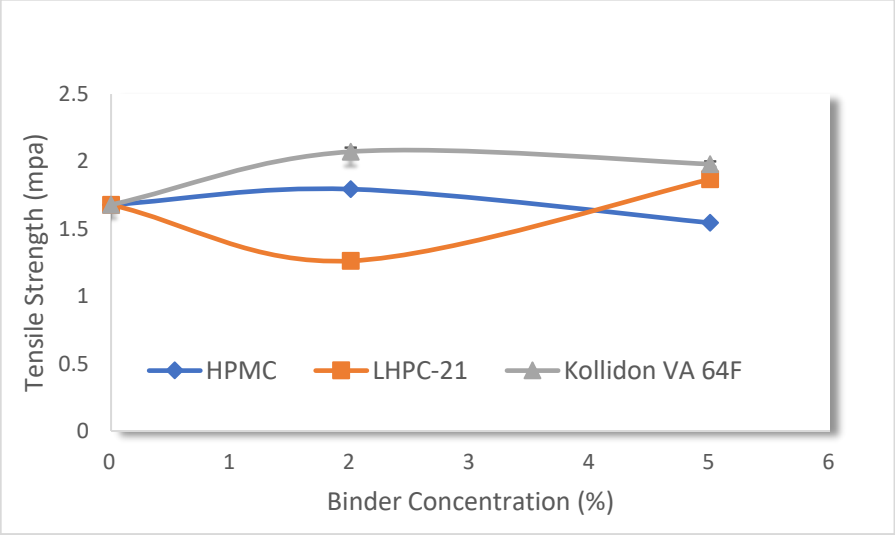


Figure 4.13 Effect of binder type and concentrations on tensile strength under 30kN force, (n=3).

In general, LHPC-21 as a binder has low tensile strength values (Di Martino, 2007). At 2 and 5% shows the same behavior as on 20kN. Maximum binder effect of LHPC-21 is seen at 5%. HPMC increased slightly in tensile strength at higher force, but kept the same behavior as seen in 20 KN.

Figure 4.14 displays the disintegration times for different binders and concentration percentages on 20kN force. Kollidon VA 64F showed that an increase in binder concentration would give an increase in disintegration times (Okoye, 2009).

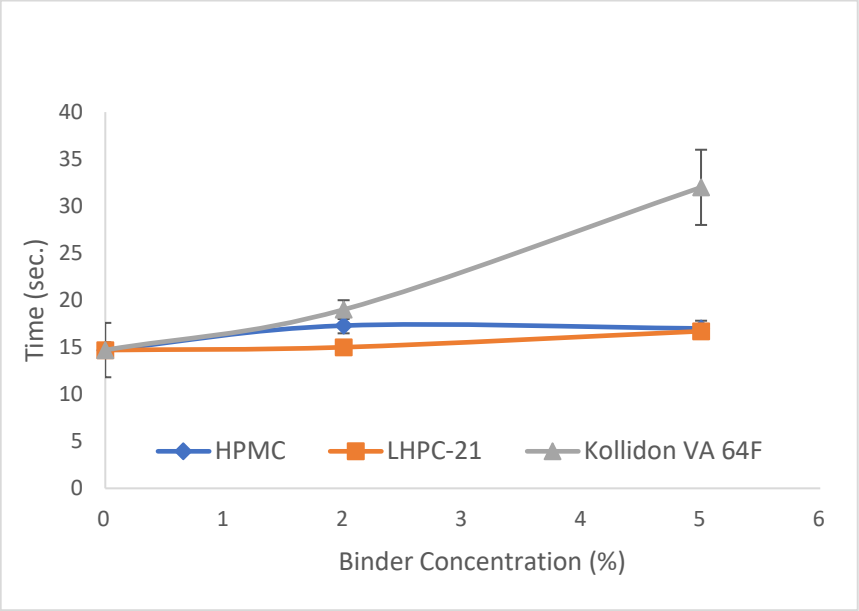


Figure 4.14 Effect of binder type and concentrations on disintegration times under 20kN force, (n=3).

HPMC which has major negative impact on disintegration time (Kolter, 2000), and LHPC-21 which has dual functions as both disintegrant and binder not only a disintegrant (Alvarez-Lorenzo, 2000), didn't show much difference in disintegration time ±0.5 seconds and had the same value of no binder formulation.

In figure 4.15 Kollidon VA 64F showed linear increase in disintegration time with increasing binder percentage and force. LHPC-21 the binder concentration didn't affect disintegration time, as the result that LHPC-21 has dual effect as binder and disintegrant.

HPMC as seen in 20 KN showed steady disintegration time at 2% and 5% binder concentrations, while at 10% slightly increase in disintegration time.

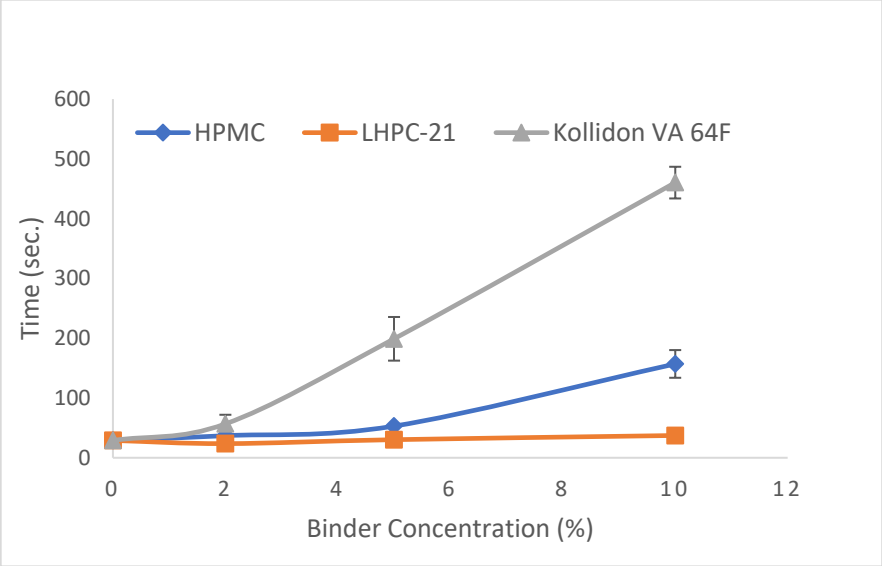


Figure 4.15 Effect of binder type and concentrations on disintegration times under 30kN force, (n=3).

Figure 4.16 shows binders effect on friability % with 20 kN applied force. Kollidon VA 64F friability results remained constant at 2% and 5% binder concentrations on 20kN, this corelated with tensile strength curves.

LHPC-21 as seen from tensile strength curve (Figure 4.12) there is a correlation with friability curve, at 2% the tablet failed in friability test, at 5 % there is a significant improvement in friability results.

HPMC failed in friability at both 2% and 5% in 20KN because it didn't show binder effect as seen before in Figure 4.12.

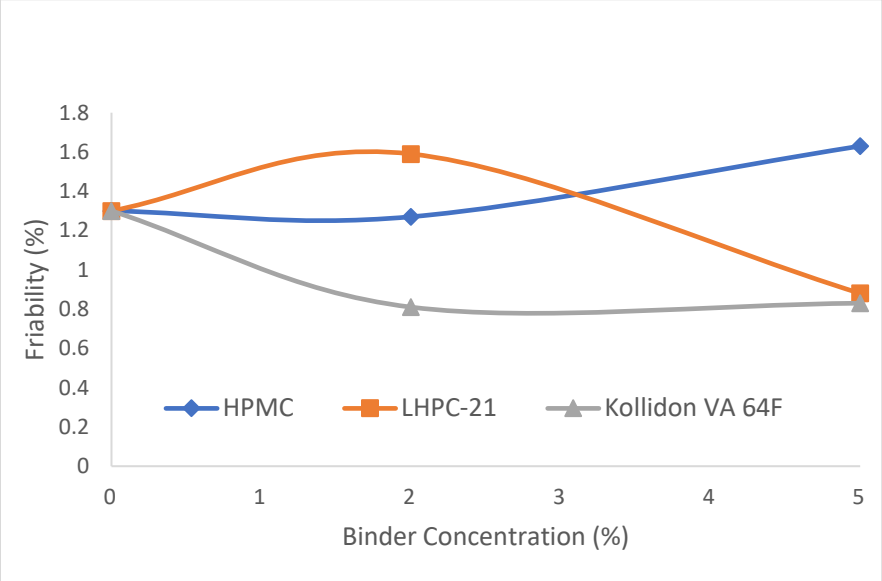


Figure 4.16 Friability % with different binders and concentrations on 20kN force, (n=5).

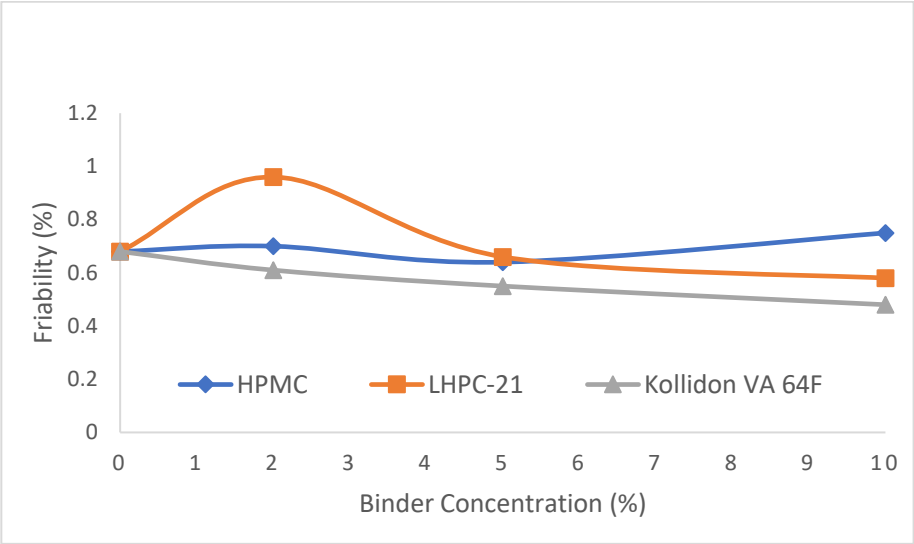


Figure 4.17 Friability % with different binders and concentrations on 30kN force, (n=5).

Figure 4.17 shows binders effect on friability % with 30 kN applied force. For all formulations increasing force to 30kN showed improved friability results. In general friability values for formulations decrease with increasing binder concentration and tensile strength (Okoye, 2009).

Kollidon VA 64F exhibit the best friability results among binders (Kolter, 2000)

LHPC-21 showed similar trend in regard to binder concentrations.

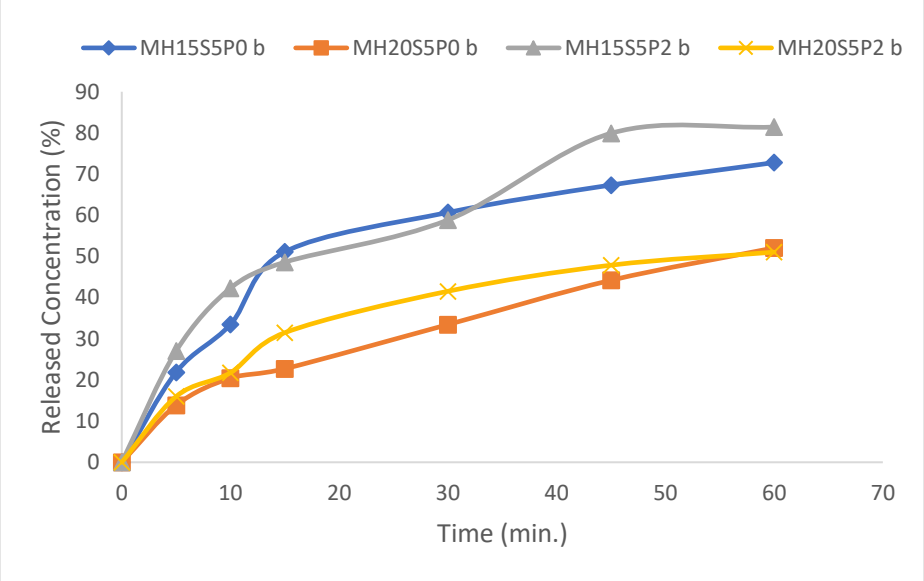


Figure 4.18 Comparative dissolution profiles of formulations containing HPMC as binder in (15, 20%) concentrations on 50 rpm, (n=3).

As seen in figure 4.18 it shows less binder concentration will give better dissolution profile and existence of Primojel® as superdisintegrant in little percentage 2% improved the dissolution profile for (MH15S5P2 b, MH20S5P2 b) little bet, but overall these results failed to pass at 30 minutes.

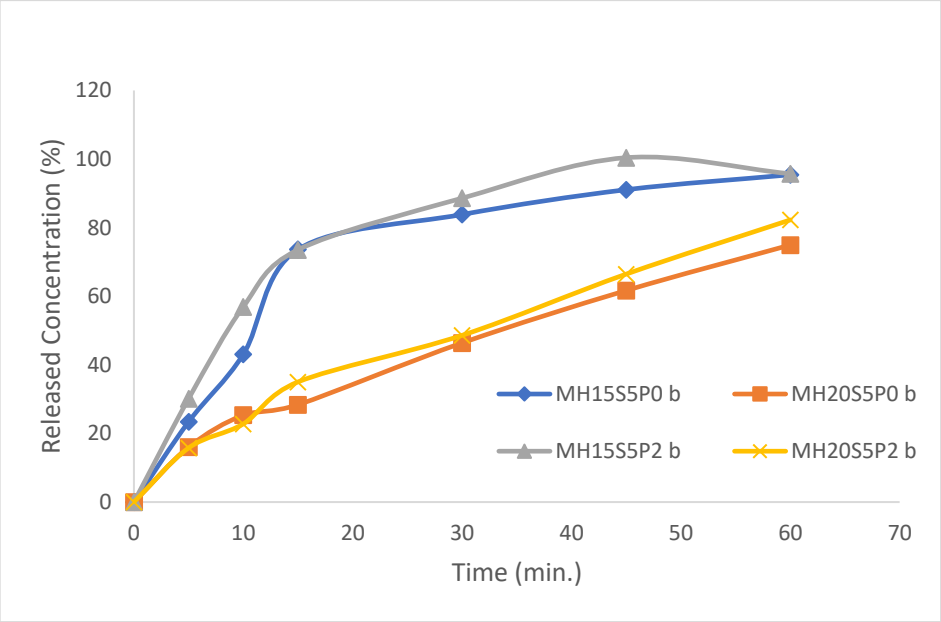


Figure 4.19 Comparative dissolution profiles of formulations containing HPMC as binder in (15,20%) concentrations on 75 rpm, (n=3).

Figure 4.19 shows similar trend as in (Figure 4.18) but for formulations containing 15% HPMC concentrations they pass after 30 minutes releasing more than 80% drug release.

The graphs in figures 4.20a, 4.20b show a comparison in dissolution profiles for two formulations with two disintegrants LHPC-21 and Starch 1500 with constant binder concentration 10% of Kollidon VA 64F on different paddle rotation speed.

On 50 rpm in figure 4.20a formulation with Starch 1500 as disintegrant which is the most commonly used disintegrant showed superior effect in comparison to LHPC-21 with the fact that both failed to pass the test at 30 minutes.

On 75 rpm in figure 4.20b it represents same trend as in 50 rpm but in exception for one formulation which contains Starch 1500 that passes the test at 30 minutes.

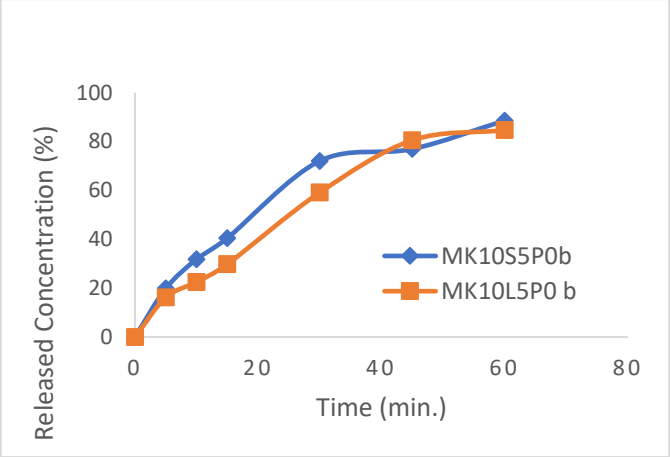


Figure 4.20a Comparative dissolution profiles of formulations containing same % of Kollidon VA 64F Binder with two type of disintegrants on 50 rpm, (n=3).

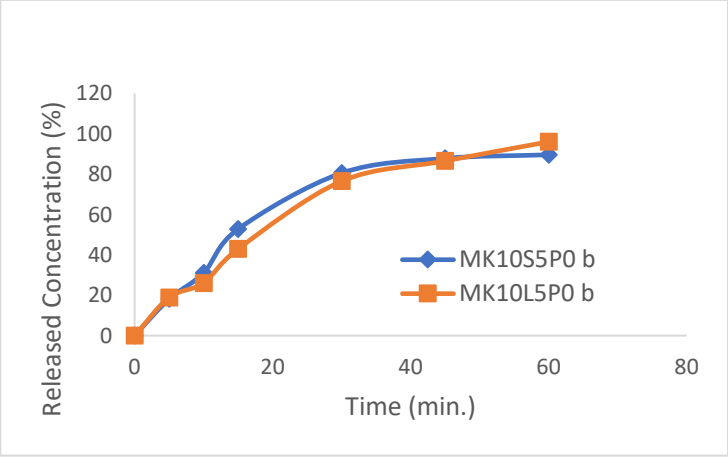


Figure 4.20b Comparative dissolution profiles of formulations containing same % of Kollidon VA 64F Binder with two type of disintegrants on 75 rpm, (n=3).

Figures 4.21a, 4.21b shows comparison in dissolution profiles for our optimum formulation and market product.

Optimum formulation dissolution profile showed slightly similar behavior according to marketed product profile, both on 50 rpm in figure 4.21a failed to pass the test at 30 minutes but passed with more than 80% at 30 minutes on 75 rpm in figure 4.21b.

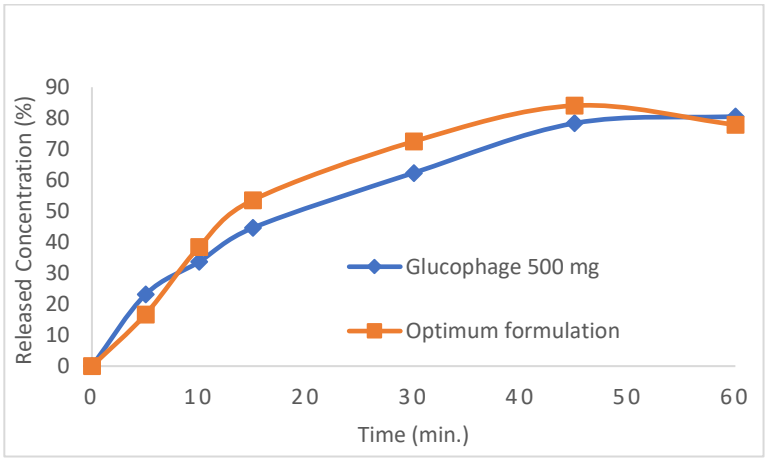


Figure 4.21a Comparative dissolution profiles of marketed product Glucophage® 500 mg and Optimum formulation on 50 rpm, n=3

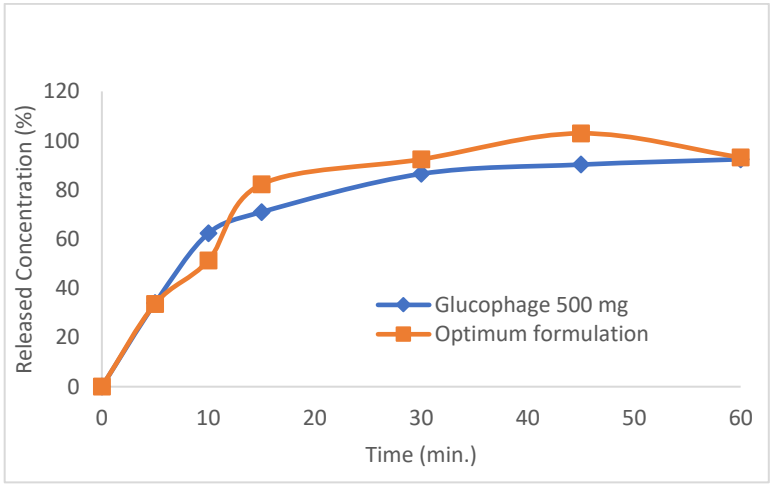


Figure 4.21b Comparative dissolution profiles of marketed product Glucophage® 500 mg and Optimum formulation on 75 rpm, n=3

CONCLUSION

The use of QbD approach by applying QTPPs and CQAs for developing Metformin HCl formulation enables us to have a higher level of assurance of tablet product quality and efficiency which is intended.

By entering quality control results of formulations which mentioned in tables (4.2a, 4.2b, 4.3a, 4.3b), we trained the program with our data.

Design space has been successfully used for the optimization of the formulation's compositions, and it enabled the prediction of optimum formulation. Design space methodology proved to be an effective tool.

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Educational Level

	Name of the Institution where he/she was graduated	**Graduation year**
Postgraduate	-	-
Masters	Near East University	2019
Undergraduate	Jordan University of Science and Technology	2017
High school	Yarmouk University Model School	2012

Job Experience

	Duty	**Institution**	**Duration (Year - Year)**
Pharmacy training		Dawacom Pharmacy /Jordan	2014
Pharmacy training		Al-Razi Pharmacy/Jordan	2016
-		-	-

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

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

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

Computer Knowledge

Program	Use proficiency
SPSS	Very good
Microsoft Office	Very good

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