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Development of an orally disintegrating mini-tablet (ODMTs) containing metoclopramide HCl to enhance patient compliance

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A Thesis

entitled

Development of an Orally Disintegrating Mini-Tablet (ODMTs) Containing

Metoclopramide HCl to Enhance Patient Compliance

by

Abdulkareem Ali Alanezi

Submitted to the Graduate Faculty as partial fulfillment of the requirements for the

Master of Science Degree in Pharmaceutical Sciences

Industrial Pharmacy Option

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Dr. Patricia R. Komuniecki, Dean College of
Graduate Studies

The University of Toledo

December 2014

An Abstract of

Development of an Orally Disintegrating Mini-Tablet (ODMTs) Containing

Metoclopramide HCl to Enhance Patient Compliance

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This research was developed and designed an orally disintegrating mini-tablets (ODMTs) containing Metoclopramide HCl, using various pharmaceutical compositions to enhance patient compliance. Metoclopramide HCl was formulated into orally disintegrating mini-tablets using the direct compression method and suitable excipients such as microcrystalline cellulose and Trehalose as the diluent, talc and magnesium stearate as lubricants. The excipients were mixed with Polyplasdone XL (crospovidone) and Primojel (sodium starch glycolate) at concentration of 3%, 5% and 7 % w/w of each using a V-Shell blender. This was done in order to select and optimize the concentration of the best superdisintegrants having the least disintegrating time and fastest dissolution. The flowability of the powder mixtures were evaluated using Carr's index, angle of repose and the Hausner ratio. The tablets were evaluated according to the USP based on weight variation, thickness, hardness, friability, disintegration time, a simulated wetting test, and in-vitro dissolution. The determination of the most effective type and optimal amount of superdisintegrants for orally disintegrating mini-tablets was manufactured by

direct compression. The final data of the study revealed that a combination of microcrystalline cellulose, Trehalose and 7% Polyplasdone XL produced the best combination after using the test previously mentioned.

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List of Abbreviations

ADHD ....Attention deficit hyperactivity disorder
AIDS ....acquired immune deficiency syndrome
API ....Active pharmaceutical ingredient

cm ....centimeter
CNS ....central nervous system
Conc. ....concentration
CTZ ....chemoreceptor trigger zone

DC ....Direct Compression
DI ....deionized

FDA ....Food and Drug Administration
FDT ....Fast Dissolving Tablet
Fig ....Figure

g ....gram
GIT ....gastrointestinal tract
GERD ....gastro-esophageal reflux disease

HCl ....Hydrochloride
HPMC ....hydroxypropyl methyl cellulose

ICH ....International Conference on Harmonization
IUPAC ....International Union of Pure and Applied Chemistry
IVIVC ....in vitro - in vivo correlation

kgf ....kilogram-force
kp ....kilopound

LBD ....Loose Bulk Density

MC ....methyl cellulose
MCC ....microcrystalline cellulose
MDT ....Mouth Dissolving Tablets
mg ....milligram

min ....minute
mL.............................milliliter
μm ....microgram
mm ....millimeter
nm ....nanometer
mol ....mole
MTH.........................Metoclopramide Hydrochloride

N................................Newton
NF ....National Formulary

ODMTs ....Orally Disintegrating Mini-Tablets
ODTs..........................Orally Disintegrating Tablets

RH ....relative humidity
rpm ....revolutions per minute

SD ....standard deviation
Sec..............................second
SGF ....Simulated Gastric Fluid
SN ....serial number
SSG ....Sodium Starch Glycolate

US ....United States
USP ....United States Pharmacopeia

5-ASA ....5-aminosalycylic acid

List of Symbols

A................................absorbance
b................................path length
c................................concentration
CO_2............................carbon dioxide
D2............................dopamine receptor
e.g. ....for example
pH............................a measure of the acidity or basicity of an aqueous solution
q.d.s. ....four times daily
R^2..............................Correlation coefficient
V_d. ....volume of distribution
V_f.............................final tapped volume
V_o. ....unsettled apparent volume

°C..............................Degree Celsius

w/w............................weight per weight

ρ_{bulk} ....Loose bulk density
ρ_{tapped}.........................Tapped bulk density
λ_{max}. ....Wavelength maximum
ε.................................molar absorption coefficient

Chapter 1

Introduction

Tablet dosage forms occupy the largest and the most significant place among all pharmaceutical dosage forms, and it considered one of the most popular drug delivery systems. The use of a glass of water to take the tablet is considered to be the easiest and most suitable technique of administration of the drug to a patient.

There are many sizes corresponding to the dose of the drug which can be given as well as the shape of the tablet. Some tablets may contain as low as 25 mg or less of the drug, and others contain 1 g. of the active per tablet, which provides a huge range of drug content. Tablet dosage forms can be made in different sizes and shapes, and the drug ingredient may contain 0.1% to 90% of a tablet bulk. It is very easy process to manufacture tablets in comparison with other dosage form. Tablet production can deliver the maximum output per manufacturing hour and is the most economical, particularly if one considers modern industrial methods including the process of direct compression (DC).

Direct Compression represents the simplest and most cost-effective tablet manufacturing technique. This technique can now be applied to orally disintegrating

tablets because of the availability of improved tablet excipients, especially tablet superdisintegrants and sugar-based excipients [1].

Orally disintegrating tablets (ODTs) can be defined as solid single-unit dosage forms that are intended to be placed in the mouth, and then swallowed without the need of water [2]. The tablet will disperse or dissolve in the saliva instantaneously, within seconds and swallowed easily as residue with no difficulty [3]. The faster the drugs disintegrate and dissolution occurs, the quicker the absorption and onset of clinical effect.

According to the US FDA, the ODT tablet was defined as "A solid dosage form containing medicinal substances which disintegrates rapidly, usually within a matter of seconds, when placed upon the tongue" [4]. It has been proven statistically that ODTs have several advantages over conventional tablets to enhance patient compliance and acceptance because of its feasibility and convenience [5]. Almost 50% of the population suffers from difficulty swallowing while taking tablets and hard gelatin capsules [6]. These populations include pediatric and geriatric populations who have difficulty swallowing large tablets. In order to overcome these problems, mouth dissolving tablets (MDT) or orally disintegrating tablets (ODT) have been developed as alternative oral dosage forms [7]. Accordingly, ODT's became an excellent choice as a new drug delivery system, because they are easy to administer and lead to better patient compliance, especially in the elderly and children [4].

The purpose of this study was to develop and design the mini-tablet and the fast-dissolving dosage form approaches to prepare orally disintegrating mini-tablets (ODMTs) of metoclopramide hydrochloride, using various pharmaceutical compositions to enhance patient compliance mainly for pediatric and geriatric patients. It is a potent dopamine

receptor antagonist used for its anti-emetic and prokinetic properties. Thus it is primarily used to treat nausea and vomiting, and to facilitate gastric emptying in patients with gastroparesis [8].

In the present study, metoclopramide hydrochloride ODTs was formulated by using the direct compression method because of convenient and cost-effective and suitable excipients such as microcrystalline cellulose and Trehalose as the diluent, talc and magnesium stearate as lubricants. The designed tablet formulations will be evaluated for according to the USP based on weight variation, thickness, hardness, friability, disintegration time, a simulated wetting test, and in-vitro dissolution. Additionally, tablets were evaluated in various temperatures and relative humidity conditions for stability.

Chapter 2

Tablet Dosage Forms

2.1 Introduction

There are many differences in physical and chemical properties between drug substances. For instance, water solubility, crystalline structure, particle size, the dose of the drug and sensitivity to hydrolysis or oxidation. Consequently, each drug molecule must be treated as an exceptional entity to itself for formulation. Limited water solubility, poor flowability, compression properties, and sensitivity to moisture and heat have been shown to an even greater extent in manufactured drugs in the last three decades. Therefore, tablet production from such molecules is a challenge. The marketplace for industrial pharmacy products demands easy and cost-effective manufacturing. There are many factors that must be considered to design and optimize a perfect and successful tablet. For example, acceptable dissolution rate, mechanically strong tablets that handle packaging, transport, and eventually patient utilization. Moreover, the tablets must fulfill the requirements for bioavailability and bioequivalency. The knowledge of excipients and the selection of the most suitable manufacturing process can achieve a successful tablet [9].

2.2 Types of Tablets

There are many excipients that can be incorporated with a drug to make a good tablet. The mechanical and chemical properties of excipients are the key point. Most of the modern tablets include mechanical strength appropriate for coating, packaging, transportation; an optimum size, shape, color for identification; and the ease of swallowing. Eventually, tablets must fulfill the requirement of the USP for drug content and release rates as well as stability and bioavailability. Based on drug delivery, tablet dosage forms can be categorized as following [9-11]:

– Simple uncoated tablets	– Fast-disintegrating tablets
– Coated tablets	– Vaginal tablets
– Effervescent Tablets	– Osmotic tablets
– Buccal and Sublingual tablets	– Controlled-release tablets
– Chewable tablets	– Multicomponent tablets
– Multilayered Tablets	– Sugarcoated tablets

2.2.1 Simple Uncoated Tablets

The simplest tablet dosage form consists of a combination of a drug and some functional excipients compressed directly. These tablets are formed by compression without difficulty using some of the pharmaceutical excipients such as binders, disintegrants, and lubricants. It should disintegrate in the stomach and become bioavailable once it used by the patient. It can be manufactured by mixing the drug and excipients in a V-shaped mixer and are compressed in a tablet press using dies and punches of suitable size.

2.2.2 Orally Disintegrating Tablets (ODTs)

It has been introduced to the market as the newest addition of tablets family. The main purpose for the development of ODTs is the potential for administration of small doses to the elderly or children who have difficulties in swallowing intact tablets. It is administered by placing it on a spoon and adding some water, in two to four seconds the tablet completely disintegrates to granules that can be swallowed easily. Orally disintegrating tablets are not only made out of special granules but can also be compressed using coated spherical pellets such as enteric-coated omeprazole pellets.

2.2.3 Film-Coated Tablets

This tablet can be coated with a polymer film to provide greater ease of swallowing, protection against light or moisture, protection of the drug from gastric acidity, and modification or control of drug release rate. It is very useful in order to identify the tablet formulation by using the color or logo. It is extremely important today not only for patient safety but also because of the problem of counterfeiting. Polymers and processes are available to achieve all of these properties.

2.2.4 Vaginal Tablets

These are tablets made to be used for insertion into the vagina for treatment of local infections or hormone replacement therapy. For instance, ornidazole and micanazole nitrate combination and estradiol hemihydrate tablets are formulated as vaginal tablets. These tablets release the drugs slowly in 20 to 30 minutes.

2.2.5 Effervescent Tablets

They are tablet that designed to dissolve or disperse quickly in water as a result of the release of carbon dioxide from the reaction between sodium bicarbonate and citric acid in the formulation. Usually they are large in terms of size and weight, with diameters up to 3 cm and weights of the order of 4 to 5 g. Although they are called tablets, the mode of administration is naturally indirect; the patients take the drug solution or suspension after dispersal. During manufacture, the formulation requires a low humidity environment, special tablet presses, and specialized lubrication for tablet ejection.

2.2.6 Buccal and Sublingual Tablets

These special tablets are intended for fast and complete drug action through dissolution in the buccal cavity or placement sublingually. As a result, the first pass effect may be avoided. They are used for hormone replacement therapy, for example, with methyl testosterone; sublingual tablets are frequently used for the delivery of isosorbide dinitrate and nitroglycerin.

2.2.7 Chewable Tablets

These tablets are designed to be chewable which cause the tablet disintegration. These tablets help to formulate a large dose of the drug, since the tablets are not swallowed immediately. Children can be convinced to take such medication, no water is required for administration, and the disintegration step for a tablet is actively achieved in the mouth before it dissolves in the gastric medium. Pediatric multivitamin or mineral

formulas, aspirin, vitamin C 1000 mg, and vitamin A 50,000 units are usually formulated as chewable tablets.

2.2.8 Multilayered Tablets

These tablets are formulated to have separate layers or a core tablet inside a tablet. In this way, two or more drugs can be kept separate in a single tablet. This complicated system has found limited applications over the years in the pharmaceutical industry. However, there is a revival of interest in the use of combination dosage forms for the treatment of diseases such as AIDS, where multiple drugs are administered each day. Tablet presses with two or three hoppers are available for the purpose of preparing multilayered dose forms. Recently, an excellent application potential was reported for compression coating, namely, the colonic delivery of drugs using pectin-hydroxy propyl methyl cellulose (HPMC) combination, which was successful for the delivery of 5-aminosalycylic acid (5-ASA), and also for peptides such as Nisin (polycyclic antibacterial peptide). This type of drug delivery system requires compression-coating equipment for mass production since a 100- mg core tablet containing the drug is surrounded by a pectin-HPMC mixture.

2.2.9 Sugarcoated Tablets (Dragees)

Sugarcoat was the major coating material before the development of film-coating processes. These tablet types generally start with a seed or core tablet that contains the drug, and the resultant coating process is a lengthy one using simple syrup, shellac, and talc, several layers of which are deposited onto the core tablet. Usually, a weight increase of as much as 100% to 300% is considered normal

2.3 Tablet Formulation Design and Pharmaceutical Excipients

Tablets are usually prepared with the assistance of appropriate pharmaceutical excipients. The formulation design of the tablet begins with a predetermined size of dose. The quantity of drug that needs to be used in a tablet can be a crucial step in formulation design. Compressed tablets commonly contain some type of pharmaceutical excipient besides the medicinal agent [12]. According to their functionality, they can be categorized as listed below [9, 13]:

- – Fillers/diluents
- – Disintegrants
- – Glidants
- – Sweeteners
- – Coating agents

- – Binders
- – Lubricants
- – Buffering agents
- – Wetting agents
- – Matrix formers

2.3.1 Fillers/Diluents

Most tablets weigh usually at least 50 mg. Therefore, fillers, diluents and/or excipients are used in tablet formulations in order to reach the desired optimum size when a drug forms a small percentage of the formula. The need of a tablet to incorporate the drug and filler is the need to increase the bulk volume and consequently the size of the tablet in order to facilitate the handling and administration of the tablet formulation. The main characteristics for an ideal filler/diluent should be [14]:

- – Chemically inert
- – Non-hygroscopic
- – Biocompatible

- Have a good biopharmaceutical properties (e.g. water soluble or hydrophilic)

- Preserve a good technical properties (such as compactability and dilution capacity)

- Have an acceptable taste

- Cheap

The following list of excipients are a summary of the most common filler/diluents that are used in most tablet formulations [9]:

- Lactose (a-lactose monohydrate, anhydrite b-lactose, spray-dried lactose)

- Microcrystalline cellulose (Avicel PH 101, Avicel PH 200, Emcocel)

- Starch (Corn starch, partially hydrolyzed starch)

- Dibasic calcium phosphate (Emcompress, Di-Tab)

- Mannitol (Parteck, Delta M)

- Sorbitol (Neosorb 60)

- Calcium sulfate (Delaflo)

- Compressible sucrose (Di-Pac, Des-tab, Nu-Tab)

Lactose is the most common filler/excipient that has been used in tablet manufacturing since it has good properties. It is water soluble; 216 mg of lactose can dissolve readily in 1 mL of water. There are three different grades of lactose: α-lactose monohydrate, anhydrous β-lactose, and spray-dried lactose that is manufactured using different drying techniques. All of them have different mechanical properties when they are used in tableting. Anhydrous β-lactose shows a steep compression force–tablet

crushing strength effect whereas the other two grades have a smaller effect. Compressibility with spray dried lactose shows its greatest effect because of its spherical granule shape. As a result, the choice of lactose grade to be chosen depends on the mechanical properties and size distribution of the which are the important factors that must be considered [9]. The main characteristics of lactose that make it a good choice are:

- pleasant taste

- non-hygroscopic

- fairly non-reactive

- good compactability

However, the main disadvantage of lactose is that some people cannot digest it easily and have lactose intolerance. For this reason, there are many alternative types of fillers to consider such as sugars or sugar alcohols. For example, glucose, sucrose, sorbitol, and mannitol, have been utilized, mainly in lozenges or chewable tablets because of their pleasant taste. Mannitol can provide a cooling feeling when it is sucked or chewed.

Starch is an important excipient for tablet and capsule formulations. It can be used as a filler/diluent, disintegrant, as well as a binder. Corn, potato, wheat, or rice are the major sources from which starch can be obtained. Starch's physical properties include: it is a white to off-white powder of a moderately coarse-to-fine nature; it is odorless, however, it is described to have a distinctive taste. It is not water soluble and contains amylose and amylopectin units. It does not flow well and cannot be compressed into a strong compact when it used in tableting. Therefore, compressible starch is produced by the partial hydrolyzation of corn starch [15]. Starch granules rupture between hot rollers in order to make pregelatinized starch. Some of the hydrogen bonding between amylose and amylopectin is partially broke during tablet manufacture to produce

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a product that contains 5% free amylose, 15% free amylopectin and 80% unmodified starch. This leads to the free amylose having disintegration properties and the free amylopectin will offer cold water solubility and improves the binding properties [15, 16]. In the comparison between all pharmaceutical excipients, it has highest equilibrium moisture content. Plastic deformation-showing materials play an important role to help the mechanical properties of starch or modified starch in tableting. In general, semisynthetic derivatives such as sodium carboxymethyl starch are an excellent disintegrant excipient when used in tablet manufacturing because of its abundance and cost effectiveness [9].

For powder dosage forms, celluloses are the most favorable choice. They are biocompatible, chemically inert and have good tablet-forming and disintegrating properties. These features allow them to be used as dry binders and disintegrants in tablet formulations. Even though celluloses are compatible with many drugs, their hygroscopicity limits their utility with many drugs that tend to hydrolyze in the solid state. Dicalcium phosphate dehydrate, an inorganic substance, is another filler or diluent that is insoluble in water and non-hygroscopic. It is primarily used in the granulation process [14].

2.3.1.1 Microcrystalline Cellulose

The development of microcrystalline cellulose (MCC) has become tremendously valuable as a tableting agent in the pharmaceutical industry [17]. It was rated as the best filler-binder choice in 1992. The reason for its preference ranged from solubility, cost, tradition, compatibility, supply, compactibility, handling, and physiological inertness [15].

Microcrystalline cellulose is described in the NF as purified, partially depolymerized cellulose, which is prepared by treating α-cellulose obtained from fibrous plants with mineral acids, producing bundles of needle-like microcrystals. MCC physical properties and appearance is as follows: this excipient is a white, crystalline powder composed of agglomerated porous particles [15, 16, 18].

It was introduced to the pharmaceutical industry in 1964 by FMC Corporation under the name Avicel PH in four different particle size grade, each with different properties [15]. As of 2014, Avicel is available in many commercial grades (see Table 2.1) for applications ranging from roller compaction, wet granulation, direct compression, superior compactibility, superior flow, high density, low moisture, and mouth-feel improvement. Its attractiveness can be recognized by its excellent compactibility at low pressures, high dilution potential and superior disintegration properties. It is observed to be chemically inert as well as compatible with most drugs. As a diluent, it is used in combination with spray-dried lactose or dicalcium phosphate dihydrate during the direct compression (DC) tableting to balance the cost or flow properties.

MCC displays a strong plastic deformation under pressure and a high dilution potential. For that reason, decent compressibility can be matched with good flow only by selecting the right grade or making a wet granulation to a certain size and shape [9]. Experimental studies show that the compactibility of microcrystalline cellulose decreased with a reduction in its moisture content using paracetamol and potassium phenethicillin as model compounds [16, 19]. The particle size of microcrystalline cellulose has a very slight effect on its compactibility. It has a high dilution potential because of its low bulk density. Mixing MCC with filler with good flowability such as α-lactose monohydrate or

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dicalcium phosphate dehydrates can help to reduce its limitation as poor flowable [16]. Experimental findings in 1979 showed that optimum tablet properties were achieved with 14% microcrystalline cellulose (Avicel PH 102), 5% sodium carboxymethyl starch (Primojel®) and 1% of both talc and magnesium stearate [20].

Table 2.1: Various Types of Avicel Microcrystalline Cellulose [21]:

Method	Product Grades	Nominal Particle Size, μm	Moisture, %	Loose Bulk Density, g/cc
Roller Compaction	Avicel DG	45	NMT 5.0	0.25 - 0.40
Wet Granulation	Avicel PH-101	50	3.0 to 5.0	0.26 - 0.31
Direct Compression	Avicel PH-102	100	3.0 to 5.0	0.28 - 0.33
	Avicel HFE*-102	100	NMT*** 5.0	0.28 - 0.33
Superior Compactibility	Avicel PH-105	20	NMT 5.0	0.20 - 0.30
Superior Flow	Avicel PH-102 SCG**	150	3.0 to 5.0	0.28 - 0.34
	Avicel PH-200	180	2.0 to 5.0	0.29 - 0.36
High Density	Avicel PH-301	50	3.0 to 5.0	0.34 - 0.45
	Avicel PH-302	100	3.0 to 5.0	0.35 - 0.46
Low Moisture	Avicel PH-103	50	NMT 3	0.26 - 0.31
	Avicel PH-113	50	NMT 2	0.27 - 0.34
	Avicel PH-112	100	NMT 1.5	0.28 - 0.34
	Avicel PH-200 LM	180	NMT 1.5	0.30 - 0.38
Mouthfeel Improvement	Avicel CE-15	75	NMT 8	N/A
	*High Functionality Excipient **Special Coarse Grade		***Not More Than	

2.3.1.2 Dicalcium Phosphate Dihydrate

It is a water-insoluble substance that used widely in the modern tablet formulation. It has a true density of 2.3 g/mL, which makes it one of the heaviest pharmaceutical excipients per volume. The compaction mechanism of dicalcium phosphate is fragile fracture, generating new surfaces, which shows much less lubricant sensitivity. This feature can be an advantage over plastically deforming materials such as MCC or some starches. It is like other inorganic salts, has a negative effect on tablet tooling.

2.3.1.3 Mannitol

It has many polymorphic forms that allow it to use as the main excipient of chewable tablets due to its negative heat of solution. This effect results in a pleasant mouth feel. D-mannitol has been reported to be superior to other polymorphs forms such as a- or b-mannitol in terms of mechanical properties and chemical reactivity. Therefore, tablets with higher crushing strengths can be manufactured. Mannitol is non-hygroscopic and shows less reactivity with drug substances. Therefore, it has a great potential to be developed more in future tablet formulations.

2.3.2 Binders

These are materials that that assist the small drug or excipient particles to bind them together to impart cohesiveness. They help to form granulate of a designed size range (commonly larger than the initial material) that flows freely and is also compressible, and eventually to be compressed into tablets or to be filled into capsules. They also help the tablet to remain intact after compression. They can be incorporated as dry powders to form a matrix that will include the drug, as in the case of dry granulation or in direct compression.

Occasionally, they are dissolved in liquids such as water or alcohol and then sprayed the powder mixture as with wet granulation. Microcrystalline cellulose is one of the materials can act as a binder/diluent when they used in the direct compression.

One of the traditional binders that use in the tablet formulation is starch. It can be used at concentrations between 5% and 10%. It disperses in cold water, and then slowly heats up to boiling with constant stirring. When a translucent paste is formed, it can be

diluted with cold water. In contrast, starch paste can be prepared with modified starch without boiling requirement boiling since it dissolves in warm water because of the free amylopectin.

In modern granulation processes starch paste can be in few applications when using high shear mixers. HPMC, MC, HPC, and ethyl cellulose can be used as binders in tablet formulations. The high-molecular weight grades of these cellulose-based materials can be used as matrix formers, and incorporated into formulations as dry binders. Ethyl cellulose is not water soluble, thus it is used as an alcoholic solution. Materials such as PVP and HPMC have largely replaced other binders such as gelatin, sucrose, simple syrup, or acacia [9].

2.3.3 Disintegrants

These are materials that facilitate the disintegration of tablets into its components either after administration in the GI tract or just in the mouth, such as in the case of the fast-disintegrating tablets. They play a significant role in the bioavailability of a drug in tablet dose forms. They swell once come into contact with water providing the force to disperse the tablet.

Based on the formulation design, higher MCC can help some to disintegrate readily during disintegration tests without an additional disintegrants. Addition of starches externally to the final granulation before tabletting is best justified for disintegration purposes. Starch is a "mild" tablet disintegrant.

Earlier there was concern that tablet compression forces should not exceed certain limits or tablet crushing strengths 70 to 80 N because of the probability of prolonged

disintegration times. However, with the developing of modern excipients, the tablets become mechanically strong with 200 to 300 N crushing strengths, and these tablets will disintegrate within five minutes or less using the super-disintegrants.

Super-disintegrants are materials can be added to tablet formulations in a range of 1% to 5% to guarantee disintegration within 1 to 10 minutes. Examples of the super-disintegrants are sodium carboxymethyl starch (ExplotabTM, Mendell, U.S.A.), cross-linked sodium carboxymethyl cellulose (PharmacelTM XL, DMV, Netherlands), and cross-linked PVP (KollidonTM XL, BASF). The rank order of the degree of swelling in water in two minutes for those disintegrants has been reported to be sodium carboxymethyl starch > sodium carboxymethyl cellulose > L-HPC 11 > cross-linked PVP > starch > MCC [9].

2.3.4 Lubricants

Modern tablet manufacturing would be difficult without Lubricant materials. They are used in the tablet formulations to reduce the friction between the lower punch and the die and the tablet. They are a mechanical necessity since friction will damage both the tablet and the tablet press during the ejection cycle.

Glidants are materials that decrease inter-particular friction, covering the particle surfaces with a thin layer to improve granule flowability. Colloidal silicon dioxide, talc, and starch can be used as glidants; colloidal silicon dioxide is effective as low as 0.5% as a glidant.

One of the important considerations of lubricants is addition to the pharmaceutical granules just before the tableting stage. The prolonged mixing with a surface-covering

lubricant such as magnesium stearate might have negative effects to the binding capacity of a granule mass which eventually can inhibit tablet formation. A strong sensitivity to lubricants can be shown on the materials that exhibit plastic deformation with a limited surface area. For this reason, the specific surface areas of a lubricant as well as the surface area of the granule mass are both significant parameters to select lubricant type, concentration, and mixing times.

Magnesium stearate is alkaline stearates and considers the most effective pharmaceutical lubricant. Its normal concentration range is between 0.1% and 2%, and its effectiveness shows a biphasic profile, a region of a fast reduction in friction up to 1 %, and a slower friction-reducing effect after 1%. It reduces the lower punch ejection force by about 70% as well as tablet tensile strength. *Stearic acid* is the second most important lubricant. It is not as effective as magnesium stearate, the minimum effective stearic acid concentration is about 1%, and it reduces the lower punch ejection force no more than 30%. It is very useful when an alkaline ingredient in a tablet formula is undesirable. In case of formulating effervescent tablets, water-soluble lubricants are essential since insoluble alkaline lubricants would accumulate on the surface of final solution or form a cloudy solution with an alkaline taste which is undesirable.

Table 2.2:   Presents the principal categories of pharmaceutical ingredients, listing some of the official and commercial agents in use [12]

Ingredient type	Definition	Examples
Buffering agent	Used to resist change in pH upon dilution or addition of acid or alkali.	● Potassium metaphosphate ● Potassium phosphate, monobasic ● Sodium acetate ● Sodium citrate, anhydrous and dehydrate

Table 2.2:   Presents the principal categories of pharmaceutical ingredients, listing some of the official and commercial agents in use (continued)

Ingredient type	Definition	Examples
Buffering agent	Used to resist change in pH upon dilution or addition of acid or alkali.	● Potassium metaphosphate ● Potassium phosphate, monobasic ● Sodium acetate ● Sodium citrate, anhydrous and dehydrate
Sweetening agent	Used to impart sweetness to a preparation Aspartame.	● Dextrose ● Glycerin ●Mannitol ● Saccharin sodium ● Sorbitol ● Sucrose
Tablet antiadherents	Prevent tablet ingredients from sticking to punches and dies during production.	● Magnesium stearate
Tablet binders	Substances used to cause adhesion of powder particles in tablet granulations.	● Acacia ● Alginic acid ● Carboxymethylcellulose sodium ● Compressible sugar (e.g.,Nu-Tab) ● Ethylcellulose ● Gelatin ● Liquid glucose ● Methylcellulose ● Povidone ● Pregelatinized starch
Tablet and capsule diluent	Inert filler to create desired bulk, flow properties, and compression characteristics of tablets and capsules.	● Dibasic calcium phosphate ● Kaolin ● Lactose ● Mannitol ● Microcrystalline cellulose ● Powdered cellulose ● Precipitated calcium carbonate ● Sorbitol ● Starch
Tablet disintegrant	Used in solid forms to promote disruption of the mass into smaller particles more readily dispersed or dissolved.	● Alginic acid ● Polacrilin potassium (e.g., Amberlite) ● Sodium alginate ● Sodium starch glycolate ● Starch
Tablet glidant	Used in tablet and capsule formulations to improve flow properties of the powder mixture.	● Colloidal silica ● Cornstarch ● Talc
Tablet lubricant	Used in tablet formulations to reduce friction during tablet compression.	● Calcium stearate ● Magnesium stearate ●Mineral oil ● Stearic acid ● Zinc stearate

Table 2.2:   Presents the principal categories of pharmaceutical ingredients, listing
some of the official and commercial agents in use (continued)

Ingredient type	Definition	Examples
Tablet coating agent	Used to coat a tablet to protect against decomposition by atmospheric oxygen or humidity, to provide a desired release pattern, to mask taste or odor, or for aesthetic purposes. Coating may be sugar, fi lm, or thick covering around a tablet. Sugar-coated tablets generally start to break up in the stomach. Film forms a thin cover around a formed tablet or bead. Unless it is enteric, film dissolves in the stomach. Enteric coating passes through the stomach to break up in the intestines. Some water-insoluble coatings (e.g., ethylcellulose) are used to slow the release of drug in the gastrointestinal tract.	●**Sugar coating** - Liquid glucose - Sucrose ●**Film coating** - Hydroxyethyl cellulose - Hydroxypropyl cellulose - Hydroxypropyl methylcellulose - Methylcellulose (e.g., Methocel) - Ethylcellulose (e.g., Ethocel) ● **Enteric coating** - Cellulose acetate phthalate - Shellac (35% in alcohol, pharmaceutical glaze)

2.4 Tablet Manufacturing Operations

There are three basic methods for tablet tablets compression: wet granulation, dry granulation, and direct compression. Most powdered medicinal agents are needed addition of excipients such as diluents, binders, disintegrants, and lubricants in order to provide the desired characteristics for tablet manufacture and efficacious use. One of the fundamental requirements in tablet manufacturing is the flowability of drug mixture from the hopper of the tablet press into the dies to enable high-speed compression of the powder mix into tablets. Powder granulations can provide this free flow, and also increase material density as well as improving powder compressibility during tablet formation [12].

2.4.1 Methods of Granulation

There are two types of granulation: wet methods, which use a liquid in the process, and dry methods in which no liquid is used. There are many different excipients will be needed to add into medicinal powder (active ingredient) in order to have a suitable formulation. The common types of excipients that used are diluents, to produce a unit dose weight of suitable size, and disintegrating agents, which are added to aid the break-up of the granule when it reaches a liquid medium. Adhesives can be used in the form of a dry powder, particularly if dry granulation is employed. These ingredients will be mixed before granulation. Figure 2-1 summarizes the sequence of unit operation used in tablets production with pre-compaction treatment by granulation.

Example of apparatus	Unit operation	Excipient
High-shear mixer	Mixing	← Filler
High-shear mixer	Agglomeration	← { Solution binder liquid
Fluidized-bed dryer	Drying	
Hammer mill	Milling	
Double cone mixture	Mixing	← { Dry binder, Disintegrant, Lubricant, Antiadherent, Glidant
Rotary press	Tabletting	
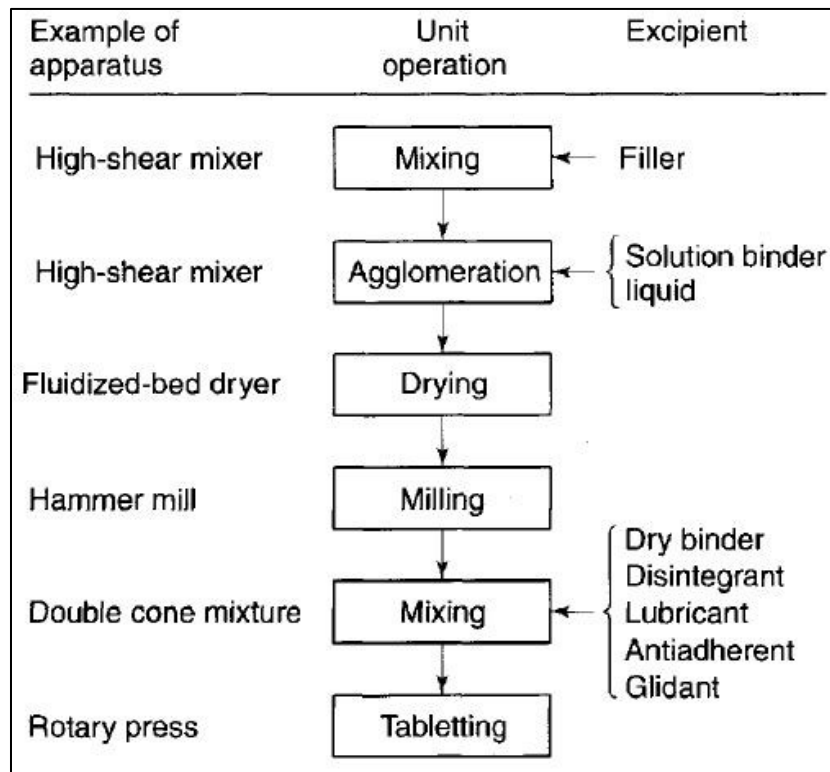
Figure 2-1:   Overview of the sequence of unit operations used in the production of tablets with pre-compaction treatment by granulation

2.4.1.1 Wet Granulation (Involving Wet Massing)

In this method, the dry *primary powder particles* using a *granulating fluid* which contains a solvent that must be volatile in order to be removed by drying, and be non-toxic. The usual fluids used during the preparation include water, ethanol and isopropanol, either alone or in combination. This granulation liquid may be used alone or, more usually, as a solvent containing a dissolved *adhesive* which is used to ensure particle adhesion once the granule is dry. Water is commonly used for economic and ecological reasons. However, might have some disadvantages as a solvent that adversely affect drug stability, causing hydrolysis of susceptible products, and it needs a longer drying time than do organic solvents. This increases the length of the process and again may affect stability because of the extended exposure to heat.

The main advantage in contrast of water is that it is non-flammable, which means the use of flameproof equipment is not required. Organic solvents are used when water-sensitive drugs are processed, as an alternative to dry granulation, or when a rapid drying time is required.

The procedure in the traditional wet granulation method involves many steps. In the beginning, the wet mass is forced through a sieve to produce wet granules which are then dried. A subsequent screening stage breaks agglomerates of granules and removes the fine material, which can then be recycled. Variations of this traditional method depend on the equipment used, but the general principle of initial particle aggregation using a liquid remains in all of the processes [14]. Figure 2-2 presents the schematic drawing of wet granulation method for tablet preparation.
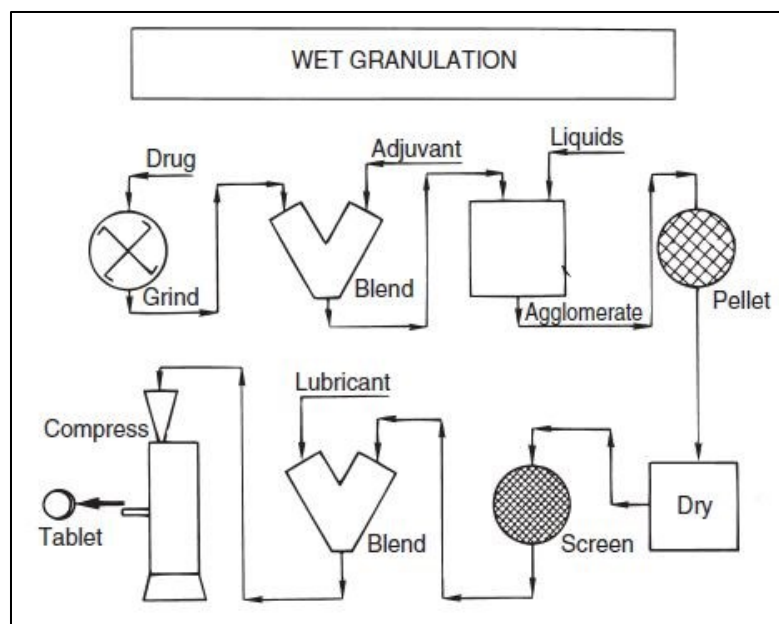
Figure 2-2: Schematic drawing of wet granulation method for tablet preparation.

2.4.1.2 Dry Granulation

In this method, the powder mixture is compacted in large pieces and then broken down or sized into granules. It is also noticed that either the active ingredient or the diluent must have cohesive properties. This method is especially applicable to materials that cannot be prepared by wet granulation because they degrade in moisture or the elevated temperatures required for drying the granules [12].

The procedure of dry granulation starts with the aggregation of primary powder under high pressure. There are two main processes. First, a large tablet (known as a *'slug')* is produced in a heavy-duty tableting press (a process known as *'slugging')*. Second, the powder is squeezed between two rollers to produce a sheet of material *('roller compaction').* In both cases these intermediate products are broken using a suitable milling technique to produce granular material, which is usually sieved to

separate the desired size fraction. The unused fine material may be reworked to avoid waste. This method is suitable to be used for drugs that do not compress well after wet granulation, or those which are sensitive to moisture [14]. Figure 2-3 presents the schematic drawing of dry granulation method for tablet preparation.
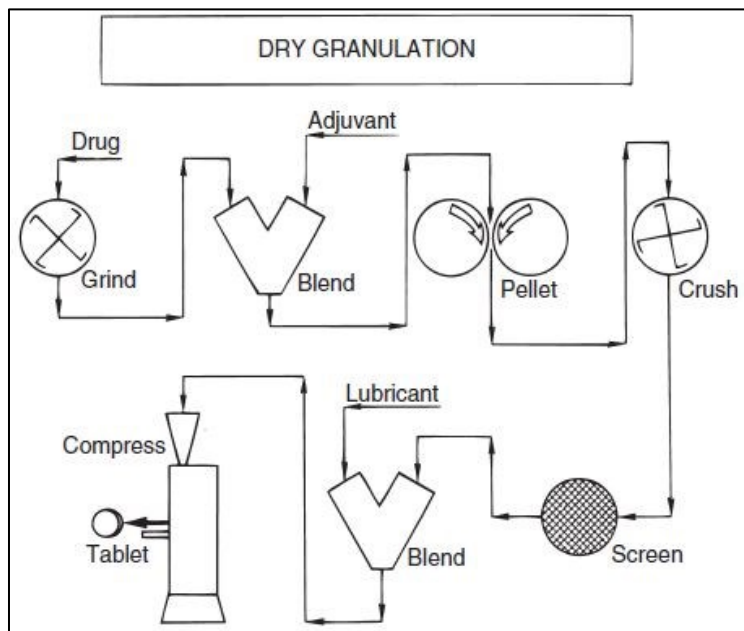
Figure 2-3: Schematic drawing of dry granulation method for tablet preparation.

2.4.2 Direct Compression (DC)

There are no further processing of powder before tableting required by this method. The powder mixture of the formulation well be mixed to ensure uniform drug distribution, and after adding a lubricant, tablets are compressed. However, the requirements for flowability and compressibility must be met by the excipients or the drug substance requires to be coated or processed. Since direct compression involves only two operations in sequence, powder mixing and compressing steps (Fig. 2-4), it is the most preferred way of making tablets, given appropriate choice of excipients.

Figure 2-5 presents the schematic drawing of direct compression method for tablet preparation. Steps in direct compression involves the following [9]:

-   Premixing drug with other ingredients using a V-shaped mixer

-   Adding a lubricant to the granules

-   Mixing with lubricant 3 to10 minutes

-   Compressing the granules
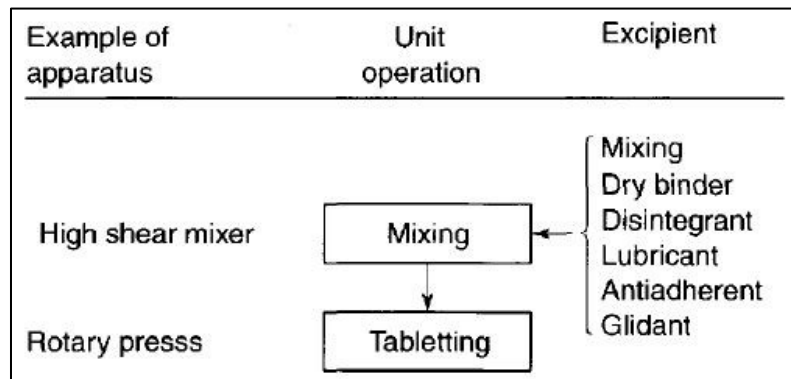
Figure 2-4:   Overview of the sequence of unit operations used in the production of tablets by direct compression
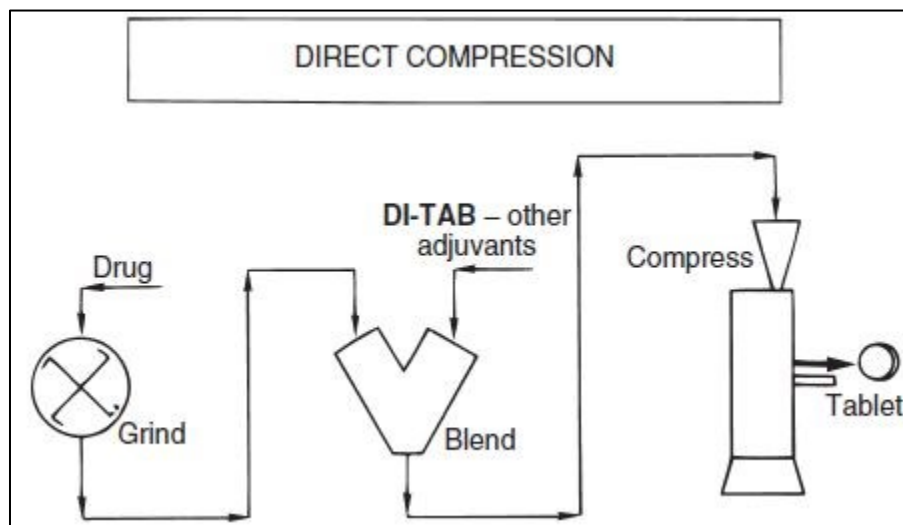
Figure 2-5:   Schematic drawing of dry Direct Compression in tablet preparation.

Pharmaceutical excipients usually do not guarantee the success of tablet formulation by using direct compression method. The active pharmaceutical ingredient (API) must have appropriate compressibility and flowability if the API represents more than one-third of tablet formulation. In that case, DC excipients may compensate for flowability and compressibility. If a drug powder have an insufficient flow and compressibility forms a large portion of a tablet, the DC method cannot be used.

Some active ingredients such as acetaminophen, amoxicillin, ascorbic acid, thiamine, and riboflavine have DC grades. Those grades are produced by coprocessing the actives with polymers such as methyl cellulose (MC), hydroxypropyl MC, acrylates, or polyvinylpyrrolidone (PVP) through a spray-drying or fluidized-bed coating process.

Compressible excipients are required in the preparation of tablet dosage form by using DC method. Microcrystalline cellulose (MCC) is the most important DC excipient. Other DC excipients include anhydrous β-lactose, spray-dried lactose, unmilled dicalcium phosphate dihydrate, pregelatinized starch, and mannitol DC. If the pharmaceutical company manufactures tablets only with DC method, it will have a lower investment cost since only powder-powder mixers and tablet presses are required.

Chapter 3

Orally Disintegrating Tablets (ODTs)

3.1 Introduction

The oral route of administration still remains as the most favored route despite tremendous innovations in drug delivery such as parenteral, transdermal, nasal, etc., [22, 23]. This is due to its various advantages such as the ease of ingestion, less pain, accurate dosage, self-medication potential, versatility and, most essentially, patient compliance [24]. It is the most frequent used route of drug delivery as well as it being generally considered to be the most convenient and economic because it carries the lowest cost [25].

These characteristics have given the oral rout to be a wide acceptance among patients and represents up to 50-60% of the total possible dosage forms [26]. The most popular solid dosage forms are tablets and capsules [27]. These solid dosage forms have a high degree of drug stability and provide accurate dosage [28]. However, some drugs can cause gastrointestinal tract irritation [29]. Difficulty in swallowing conventional tablets is one of the essential problems of this dosage form. Additionally, pediatric and geriatric patients also experience difficulty and inconvenience of swallowing [24]. Since drinking water plays an important role in the swallowing of oral dosage forms, patients might experience an inconvenience to swallow the tablet when water is not available, such as in

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the case of motion sickness (kinetosis), sudden episodes of coughing during the common cold, allergic conditions and bronchitis. For these reasons, tablets that can rapidly dissolve or disintegrate in the oral cavity have attracted a great deal of attention [27].

Orally disintegrating tablets (ODTs) can be defined as solid single-unit dosage forms that are intended to be placed in the mouth, and then swallowed without the need of water [2]. The tablet will disperse or dissolve in the saliva instantaneously, within seconds and swallowed easily as residue with no difficulty [3]. The faster the drugs disintegrate and dissolution occurs, the quicker the absorption and onset of clinical effect. Lozenges, buccal, and chewable tablet are also some of solid oral dosage form that can be used without water intake. However, there are differences in the drug release methodology between them. In comparison to ODTs, Lozenges and buccal tablets are intended to dissolve slowly in the mouth, whereas, chewable tablets have a longer disintegration time and require chewing action by the patients before they can be swallowed [30]. ODTs have become a favored alternative to conventional oral dosage forms such as tablets and capsules and other liquid pharmaceutical preparations over the past three decades [31]. Orodispersible tablets, rapidly disintegrating tablets, fast dissolving tablets, mouth dissolving tablets, melt-in-the-mouth, fast dissolving drug delivery, quick dissolving tablets are some of the names that have been used as synonyms for orally disintegrating tablets [22]. The European pharmacopoeia approved term was "orodispersible tablet". They defined it as a tablet that is placed in the mouth where it disperses rapidly before swallowing [3].

According to the US FDA, the ODT tablet was defined as "A solid dosage form containing medicinal substances which disintegrates rapidly, usually within a matter of

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seconds, when placed upon the tongue" [4]. It has been proven statistically that ODTs have several advantages over conventional tablets to enhance patient compliance and acceptance because of its feasibility and convenience [5]. Almost 50% of the population suffers from difficulty swallowing while taking tablets and hard gelatin capsules [6]. These populations include pediatric and geriatric populations who have difficulty swallowing large tablets. In order to overcome these problems, mouth dissolving tablets (MDT) or orally disintegrating tablets (ODT) have been developed as alternative oral dosage forms [7]. Accordingly, ODT's became an excellent choice as a new drug delivery system, because they are easy to administer and lead to better patient compliance, especially in the elderly and children [4]. Orally disintegrating tablets have become very attractive for even active people who do not suffer from any swallowing problems [26]. Specialized peel-off blister packaging is required for fast dissolving tablets since they are very fragile and friable. ODT technologies have been developing very rapidly over this past decade. There are new generations of ODT which have been advanced to overcome the limitations of the earlier products. Some companies provided technologically advances to produce pleasant tasting tablets to overcome the common problem of poor drug taste which compromised the benefits of the ODT. Other companies developed new technologies to improve the controlled release of ODT. The ease of manufacture and fewer risks associated with fast dissolving tablets have made ODT technology an excellent choice for most pharmaceutical manufacturing. Another factor which makes ODTs highly favorable is the route of administration that it has only administered by mouth. This one factor allows other companies to get approval for a generic version of the drug [4].

3.2 Criteria for Orally Disintegrating Tablets

– ODT's dissolve/disintegrate within a few seconds once placed in the mouth, which as a result can be taken with or without the requirement of water [1, 22, 23, 31-33].

– They are compatible with taste masking and other excipients [1, 22, 31-33].

– ODTs have pleasant mouth feel and leave minimal or no residue in the mouth. This can be very helpful in order to avoid the bitter taste of the drugs, particularly for pediatric patients [1, 22, 23, 31-34].

– ODTs provide good stability since they exhibit less sensitivity to environmental conditions [1, 22, 31-34].

3.3 Desirable Characteristics of Fast Dissolving Drug Delivery System

ODTs illustrate some ideal characteristics which differentiates them from other dosage forms such as conventional tablets. Some of these significant desirable characteristics include the following [22, 34]:

– Effective cost due to lower production, simple packaging and distribution costs compared to other commercially available products [1, 22, 23, 31-34].

– Convenient to administer specially for patients who refuse to swallow including pediatrics and geriatrics, and other groups who might experience difficulties using conventional oral dosage form such as the mentally disabled, stroke victims, bedridden, affected by renal failure and uncooperative patients [2, 7, 22, 26, 27, 32, 34].

– Adequate enough strength to resist the rigors of the manufacturing process and post manufacturing handling [1, 33].

– Provides accurate dosing compared to other dosage forms such as liquids, since they are units of solid dosage forms, which allows high drug loading and an ideal alternative for pediatric and geriatric patients [1, 22, 31-34].

– Has a rapid onset of action which will produce fast dissolution and absorption of the drug in the oral cavity [2, 7, 22, 27, 32].

3.4 Common Conditions for ODTs Indications [4, 35]

– Pain, fever, heartburn, diarrhea, migraine, anxiety, insomnia for fast faction.

– Parkinson's disease, Alzheimer's disease, psychosis, Schizophrenia, Hypertension, Cholesterol, Transplantation to improve patient's compliance.

– Cough, cold, allergy, pain, fever, ADHD that can be associated with pediatrics.

3.5 Advantages of ODTs as Drug Delivery System [4, 6, 36]

– Pregastric absorption from the mouth, pharynx, and esophagus as the saliva passes down into the stomach can result in enhancement of bioavailability which leads to a reduced dosage and improves the clinical performance and reduces the side effects [2, 7, 22, 27, 31-33].

– It is useful for some conditions that need a rapid action such as motion sickness, sudden episodes of allergic attack or coughing [2, 22, 26, 27, 32, 34].

– Highly convenient for patients who are traveling anywhere, anytime and do not have instant access to water [2, 7, 23, 26, 27, 31].

– Provide a suitable drug delivery for some drugs that have low molecular weight and are highly permeability [31].

– Cost effective for manufacturing because they require a minimum number of ingredients [31].

– Due to rapid disintegration and dissolution time, orally dissolving tablets increase the bioavailability of insoluble and hydrophobic drugs [7, 23, 26, 27].

– Improve patient safety administration by avoiding the risk of chocking or suffocation during oral administration due to physical obstruction [2, 22, 27, 31, 32, 34].

– ODTs have a unique feature by combining the advantage of solid and liquid dosage forms. They provide long term stability for the solid dosage form and high bioavailability as a liquid dosage form when placed on the mouth [2, 7, 26, 27].

– Useful for pediatric, geriatric and psychiatric patients because there is no need for chewing [7].

– Medications with a bitter taste have taken advantage of ODT technologies by the use of flavors and sweeteners to make them as pleasing as possible when they dissolve in the mouth [22, 31-33].

– The new ODT patented technologies allow the incorporation of microencapsulated drugs for enhanced bioavailability, flexibility of dosing and immediate and/or controlled release [7].

– As ODTs are unit solid dosage forms, they provide ease of handling by the patients [22, 31, 32].

– ODT technologies show multipurpose utilization, therefore they are suitable for the development of enhanced products for veterinary medicines, OTC, as well as prescription medicines [34].

– Orally disintegrating tablet technologies have been expanded to provide a new business opportunity demonstrating product differentiation, product promotion, patent extensions and life cycle management [22, 27, 32-34].

3.6 Limitation of Mouth Dissolving Tablets [7]

- Insufficient mechanical strength that make ODTs difficult to handle
- Some of ODTs may leave unpleasant taste or gritty feel in the mouth if they not formulated properly

3.7 Drug Selection Criteria [27, 37]

– Dose should be lower than 20 mg for FDT.

– Drug should be partially nonionized at pH in oral cavity.

– Drug should be diffuse and partition into the epithelium of the upper GIT (log P > 1, or preferably >2)

– Drug should have to permeate through oral mucosal tissue.

3.8 Ideal Drugs which are Used in ODT [27]

– Analgesic and Anti-Inflammatory Agents: Ibuprofen,

- Proxicam, Mefenamic Acid

- Anti-bacterial Agent: Erythromycin, Tetracycline,

- Doxycycline.

- Anti-fungal Agents: Griseofulvin, Miconazole

- Anti-Malarial: Chlorquine, Amodiaquine

- Anti-Gout Agent: Allopurinol, Probenecid

- Anti-Hypertensive: Amlodipine, Nefidipine

- Anti-Coagulants: Glipizide,Tolbutamide

- Anti-Protozoal Agents: Benznidazole, Tinidazole

- Anti-Thyroid agent: Carbimazole

- Cardiac Inotropic Agent: Digitoxin, Digoxis

- Gastro-Intestinal Agents: Omeprazole, Ranitidine, Famotidine

- Nutritional Agents: Vitamin A, Vitamin B, Vitamin D etc

- Oral Vaccine: Influenza, Hepatitis, Polio, Tuberculosis etc

3.9 First Generation ODTs

First generation of ODT was manufactured to make the tablet dissolve rapidly in the mouth and provide ease of swallowing and convenience for patients. It was very successful in the pharmaceutical market. However, did not take long that the pharmaceutical industry realized the dosage form of ODT is not applicable for some drugs. For instance, the amount of active pharmaceutical ingredient (API) should be low to consider as a choice of ODT. This obstacle and others had opened the door for the

scientists to search for a novel technology that can adapt and solve some of the issues that accompanied with the first generation.

Some of the main features of first generation ODTs are high porosity, low density, and low hardness which allow them to be brittle and difficult to handle. Freeze-dried technology produces very friable ODT making them very difficult to package traditionally and taking some consideration regarding storage stability. Consequently, high production costs will be required with blister packaging which is often used allowing them to be less convenient comparing with other packaging such as bottles. Another difficulty with first generation is bitter taste of the drugs. It was found that very hard to mask the poor taste by traditional flavoring and sweetening agents which restrict their usage. Nowadays, there are some novel technologies on the pharmaceutical market that can provide effective taste-masking capabilities. One of the technologies in the market is coacervation (encapsulation) technique. Pharmaceutical companies are looking for more utilization out of the ODT dosage forms. They are trying to improve the quality of ODT by solving the issues of the first generation such as higher API loading, more effective taste masking, controlled-release capability, low friability, cost-effective development, and more packaging options [4, 38].

3.10 New Generation ODTs

New generations of ODTs has enhanced taste masking, allowed a modified-release profile, and improve the bio-availability. High load of APIs and mask extreme poor taste drugs had achieved which eventually expand the range of therapeutic

applications of ODTs. The new technologies of ODTs contain rapidly dispersing micro-granules, a direct compression blend, and an external tablet lubrication method. One of the characteristics of the new generation is an excellent physical strength to handle transportation with a friability test of less than 0.5 percent allows them to be packaged in bottles or blister packs. Other features such as mouth-feel and disintegration properties. They were able to achieve 15 to 30 seconds of disintegration and provide a smooth, pleasant tasting mixture of API granules and carrier that is easily swallowable.

Micro-encapsulation has combined effectively on ODT technology to create a mask that handle extreme APIs bitter taste and utilized in soluble and poorly soluble substances, as well as to high-dose products. Coacervation technique used to encapsulate the drug particles completely and provides superior taste masking. It applied directly by covering the dry crystals or granules of the drug with a uniform coating of polymeric membranes of varying thicknesses and porosities. This will create a granules ranging from 105 to 300 microns that have a membrane that act as an inert barrier between the API and the taste buds and a stabilization barrier between the API and the tablet excipients. This technique used widely to mask has taste-masked some of the extremely poor-tasting drugs. However, there are still some challenges for ODTs such as using polymers as a taste mask to achieve bioequivalence. The polymers can inhibit the drug release in the GI tract and delaying the onset of action. Using a micro-encapsulation technique restricts dissolution of the API in the mouth, but allows rapid dissolution in the GI tract, therefore overcoming the bio-equivalence obstacle as given in Figure 3-1[4, 38].
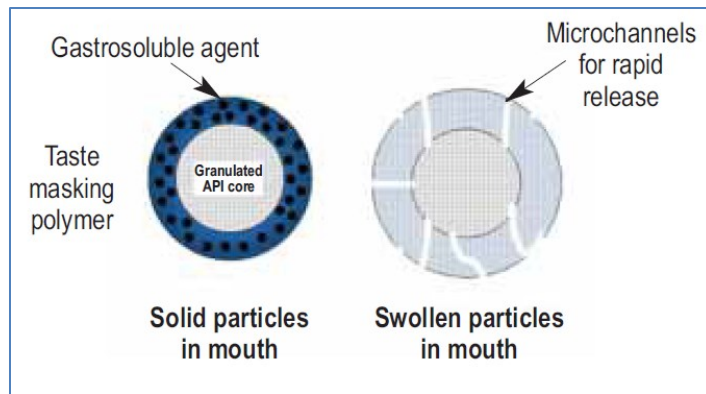
Figure 3-1:   Microencapsulation restricts dissolution of API in mouth but allows rapid dissolution in the GI Tract.

3.11 Pharmacokinetics of ODTs

Drug will be absorbed and reach the therapeutic level and release the pharmacological action once it placed on the moth. Therefore, the rate and extended absorption are very important. Conventional dosage form of tablet has a longer disintegration time will eventually leads to delay in the dissolution release. In contrast with ODTs, the disintegration time and dissolution release are much faster. The absorption will start on the mouth, and then pharynx and esophagus until the saliva reach the stomach.

Age, gastrointestinal tract (GI) pH, blood flow through GI tract are some factors that should be taken into consideration when prescribing ODTs especially for old population since they tend to have a decrease in body mass and total body water, which eventually lead to a reduction in volume of distribution (V_d) for water soluble drugs whereas the opposite to lipid soluble drugs, the volume of distribution will be increased. Another factor also for such population is liver volume. It will decrease and as a result the blood flow to the liver will reduce the bio-transformation of the drug through

oxidation, reduction, and hydrolysis. All these factors will affect the elimination by renal

clearance and the half-life increase as well [4].

Chapter 4

Orally Disintegrating Tablets Technologies

4.1 Approaches for Fast Dissolving Tablets

ODTs have fast dissolving property that related to the quick entry of water into the tablet matrix which eventually leads to very rapid disintegration. For this reason, the main approaches to develop orally disintegrating tablets include maximizing the porous structure of the tablet matrix, incorporating the suitable disintegrating agents, and using highly water-soluble excipients in the formulation [4, 7].

4.2 Various Techniques Used in ODTs Manufacturing

4.2.1 Freeze Drying/ Lyophilization

Freeze-drying is a process in which water is sublimated from the product after it is frozen. This technique forms the basis of Zydis, Qucksolv, and Lyoc technologies, which are used to manufacture rapidly dissolving tablets. This procedure will produce a product that has highly porous, with a very high specific surface area that dissolve rapidly and show enhancement in absorption and bioavailability [4]. The drug should have a particle size < 50µm [6, 39], the dose should not exceed 60 mg for water soluble drugs, and 400 mg

for water insoluble drugs. The ODTs manufactured by lyophilization usually consist of the following excipients:

- Polymers (e.g., gelatin, alginates, and dextrin) to enhance the strength and rigidity of the tablets.

- Polysaccharides (e.g., mannitol and sorbitol) to improve the palatability.

- Collapse protectants (e.g., glycine) to prevent the drugs from shrinking in the package during the manufacturing and storage.

- Flocculating agents (e.g., xanthan gum and acacia) to deliver uniform dispersion of the drug particles.

- Preservatives (e.g., parabens) to inhibit the microbial and fugal growth.

- pH adjuster (e.g., citric acid or sodium hydroxide) to optimize chemical stability.

- Flavors and sweeteners to improve patient compliance.

- Water was added to ensure formation of the porous units.

Freeze-drying consists of multiple steps. In the beginning, the active ingredient dissolved or dispersed in an aqueous solution of a carrier. Then, the mixture is dosed by weight and poured to the blister packs that have the wells. Then, the blister packs hold by a tray that will pass through a liquid-nitrogen freezing tunnel to freeze the drug solution or dispersion. The frozen blister packs will be placed in the refrigerated cabinet to continue the freezing forces and then exposed to freeze-drying. Aluminum foil backing is applied on the blister-sealing machine. Eventually, the blisters are packaged and shipped.

Lyophilization method is relatively expensive and time consuming. This method also has problem with products to use conventional packaging because they are very fragile. It provides poor stability of the products under stressed conditions [1].

4.2.2 Tablet Moulding

In order to make the tablet dissolved completely and rapidly, molded tablets always contain water soluble ingredients and the APIs usually absorbed through the mucosal lining of the mouth. Following are the different tablet moulding techniques:

A. *Compression Moulding Process*: The powder blend of the tablet will be moistening with hydroalcoholic solvent that followed by compression force lower that that used in the manufacturing of conventional tablets into mold plates to form a wetted mass. Finally the solvent will remove by air drying to yield tablets that possess a very porous structure that accelerate the dissolution process [1].

B. *Heat-Moulding Process*: Heat molding process is another for to prepare tablet by molding. It utilizes an agar solution as a binder and a blister-packaging well as a mold. It starts with a suspension preparation that contains drug, agar, and sugar (e.g., mannitol or lactose). The suspension will be poured into the blister packaging well until the agar will be solidified at room temperature to form a jelly, and eventually dried around 30 ºC under vacuum [33].

4.2.3 Spray Drying

This technique used in the pharmaceutical industry to produce highly porous powder. An experimental studies have reported this process to produce mouth dissolving

tablets [40]. In that experiment, the formulation used hydrolyzed and unhydrolyzed gelatin as a support agent for the mixture, mannitol as a bulking agent, sodium starch glycolate or crosscarmellose as a disintegrants. Acid (e.g., citric acid) or alkali (e.g., sodium bicarbonate) can be added to enhance the disintegration time and the dissolution. Finally, the formulation was spray-dried to produce a very porous powder to tablet that disintegrates in less than 20 seconds in an aqueous medium [1, 4].

4.2.4 Melt Granulation

In this technique, the pharmaceutical powders are efficiently agglomerated by a meltable binder. The advantageous of this method is that no water or organic solvents will be involved which means there is no drying step. Therefore, this process is less time consuming and uses less energy in wet granulation. This technique can be very useful to improve the dissolution rate of poorly-water soluble drugs such as griseofulvin [7].

4.2.5 Sublimation

This process using volatile substances such as urea, urethane, camphor etc., to the other excipients and the powder mixture compressed. After compression, the volatile materials are removed by sublimation from the compressed tablet. The result will be a very porous tablet due to the formation of the pores where camphor particle to be present before the sublimation. The yield tablet product with high porosity will disintegrate in 15 seconds when it is placed in the mouth (approximately 30%). There are some solvents that can also be used to form pores in the tablet like cyclohexane, benzene in addition to the other excipients. This technique has helped to develop a highly porous structure of

ODTs with a good mechanical strength. Figure 4-1 summarizes the steps that used in the

sublimation procedure [41-43].
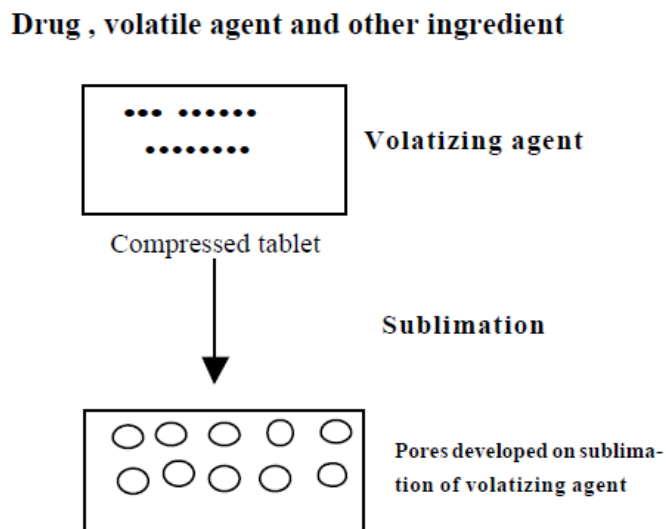
Figure 4-1: Steps involved in the sublimation technique of fast dissolving tablet.

4.2.6 Direct Compression

For most pharmaceutical companies, direct compression method represents the

simplest and most cost effective tablet manufacturing technique. They can use the

conventional manufacturing equipment because of the improved excipients especially

superdisintegrants and sugar based excipients that made this technique to be more reliable

in the ODTs preparation to provide good physical resistance and a quicker disintegration

time [44].

A. *Superdisintegrants:*   The addition of superdisintegrants on most of ODT

technologies that used by direction compression has dramatic effects to achieve a paid on

both the disintegration and dissolution times [2, 45].   Water-soluble excipients and

effervescent agents can further accelerate the process of disintegration time when they

add to the formulation ingredients. The following of non-effervescent disintegrants are used in the pharmaceutical manufacturing using in by direct compression methods [46]:

- *Starch and modified starches*: This group includes natural starches (such as maize starch and potato starch), directly compressible starches (such as starch 1500), modified starches (such as carboxymethylstarches and sodium starch glycolate), and starch derivatives (such as amylose).

- *Cross-linked polyvinylpyrrolidone*

- *Modified celluloses* such as cross-linked sodium carboxymethylcellulose

- *Alginic acid and sodium alginate*

- *Microcrystalline cellulose*

- *Methacrylic acid-divinylbenzene copolymer salts*

B. ***Sugar Based Excipients:*** they have been used widely to manufacture ODT by direct compression. There are many sugar based excipients such as dextrose, fructose, isomalt, lactilol, maltilol, maltose, mannitol, sorbitol, starch hydrolysate, polydextrose and xylitol that are used on ODTs preparation. They have many characterize with high aqueous solubility and sweetness, and hence provide taste masking property and a pleasing mouth-feel effect. Therefore, almost most of the ODTs formulations incorporate some sugar materials as bulking agents. Sugar based excipients can be classified into two types on the basis of molding and dissolution rate [26]:

- Type 1 saccharides (lactose and mannitol) exhibit low mouldability but high dissolution rate

- Type 2 saccharides (maltose and maltilol) exhibit high mouldability and low dissolution rate.

An experimental formulation has developed an ODT based on insoluble inorganic excipients as the main components. According to the patent, there are two main factors affecting the time of the disitegratoin of ODTs:

- The quantities of the disintegrant and insoluble inorganic excipients are used.

- The relative weight ratio between the water insoluble and soluble excipients in case of using water soluble excipients

According to the study, a strong tensile strength and low friability can be achieved with sufficient compression force. It was found that the disintegration time was not significantly affected by the high compression force. In the formulation, three major components were used:

- **Substantially water insoluble components**. This group includes water-insoluble of excipients, drugs (either coated or uncoated), lubricants, and glidants. The water-insoluble excipients include insoluble inorganic salt (e.g., di- or tri-basic calcium phosphate) or organic filler (e.g., microcrystalline cellulose).

- **Substantially soluble components**. This group includes compressible sugars, flavoring agents, sweeteners, binders, and surfactants.

- **Disintegrants**. Such as maize starch or modified starch, cross-linked polyvinylpyrrolidone, or sodium carboxymethylcellulose.

The study was concluded that the disintegration time increased as the amount of insoluble component decreased. If the active ingredient was only a small portion of the whole formulation, the disintegration time could be optimized by including insoluble fillers (e.g., microcrystalline cellulose and silicon dioxide) or by increasing the amount of insoluble inorganic excipients (e.g., calcium salt such as dibasic calcium phosphate) [26].

45

4.2.7 Mass Extrusion

This technique was used the solvent mixture of water soluble polyethylene glycol in order to soften the active blend, after that used methanol and the expulsion of softened mass through extruder or syringe to produce a cylindrical shape of the product into equal segments by using heated blade to form the tablet. The dried cylinder can also be used to coat granules of bitter tasting drugs to achieve taste masking [4, 26, 47].

4.2.8 Taste Masking

In this method, the drugs are microencapsulated into pH sensitive acrylic polymers (e.g., Eudragit E, Eudragit L-55 and Eudragit RL) to mask the bad taste using solvent evaporation and solvent extraction techniques. These polymers help to mask the bitter taste of the medications and increase the dissolution rate and bioavailability for the ODTs compared to conventional tablets. A novel technique for taste masking of macrolides was reported by using monoglycerides. These materials are selected for the drugs with unpleasant taste. They have a low melting point which can form good elaborate film, easily soluble in intestine [27, 48].

4.2.9 Cotton Candy Process

This technique also known as the candy floss process, it utilizes an inimitable spinning mechanism to yield floss-like crystalline structures that mimic cotton candy. The orally disintegrating tablets are formulated by using candy floss. Flash melting and spinning will produce a matrix of polysaccharides or saccharides which partially recrystallized to have improved flow properties and compressability. The candy floss

matrix will blend and mill with the active ingredients and other excipients, and eventually compressed to produce the ODT. This process can be used with larger drug doses and offer improved mechanical strength [42]. The manufacturing procedure involved four steps:

    1. Floss blend   2. Floss processing

    3. Floss chopping and conditioning   4. Blending and compression

4.3 Patented Technologies for ODTs preparation

4.3.1 Zydis Technology

It was the first marketed technology developed by R.P.Scherer Inc., to produce orally disintegrating tablets. The tablet disintegrates and dissolves in the mouth within seconds once it placed upon the tongue. The freeze dried (lyophilized) structure disintegrates does not require water for swallowing.

The drug is entrapped or dispersed in a matrix that composed consist of two components, a saccharide (e.g. mannitol) and a polymer (e.g. gelatin) to form a unique dried tablet. The polymers (e.g. gelatin, dextran) are added to provide strength during handling and as collapse protectant to prevent the shrinkage during the manufacturing process and long-term storage. The saccharides (e.g. mannitol, sorbitol) are added to form a crystallanity, elegance, and hardness. There are some other excipients can be added such as flocculating agents (e.g, xanthan gum and acacia) to provide uniform dispersion of drug particles and inhibit the sedimentation during manufacturing process; preservatives (e.g., parabens) to prevent microbial growth; permeation enhancers (e.g., sodium lauryl sulphate) to improve permeability; pH adjusters (e.g, citric acid) to

optimize chemical stability; flavors and sweeteners to improve patient compliance [23, 49].

Table 4.1 illustrates the basic formulation composition that used in Zydis technology.

Microencapsulation technique also used to mask the bitter taste of the drug by utilizing

special polymers and resins.

Tablet 4.1: Basic formulation composition that used in Zydis technology

Formulation function	Typical component
Matrix former	Gelatin (Bovine, Fish), non-gelatin polymers
Structure former	Mannitol
Structure promoter	Gycine
Sweeteners	Aspartame, Acesulfame K
Others excipients	Flavors, pH modifier, colors

Water was used in the manufacturing process to ensure that of porous product was

achieved for rapid disintegration. The yield product has a very light weight and fragile,

and must be dispensed in a special blister pack [42, 50]. Zydis technology provides the

advantages of a liquid medication in the form of a solid preparation. This advantage

improved patient compliance and convenience by making the drugs available at any time

to be used without the presence of water. The formulation allows pre-gastric absorption

which eventually improves the bioavailability for some water soluble drugs. This can

help to reduce the dosage and prevent adverse effects. Zydis formulation should be used

within six month from opening [6]. Figure 4-2 illustrates the schematic drawing of Zydis

process. There are some disadvantages that associated with Zydis technology. It is a

relatively expensive manufacturing process. Since it is very light weight and fragile, it

should not be stored in backpacks or the bottom of purses. It has poor stability at higher

temperatures and humidity. It readily absorbs water; therefore it is very sensitive to

degradation at humidity greater than 65% [4].
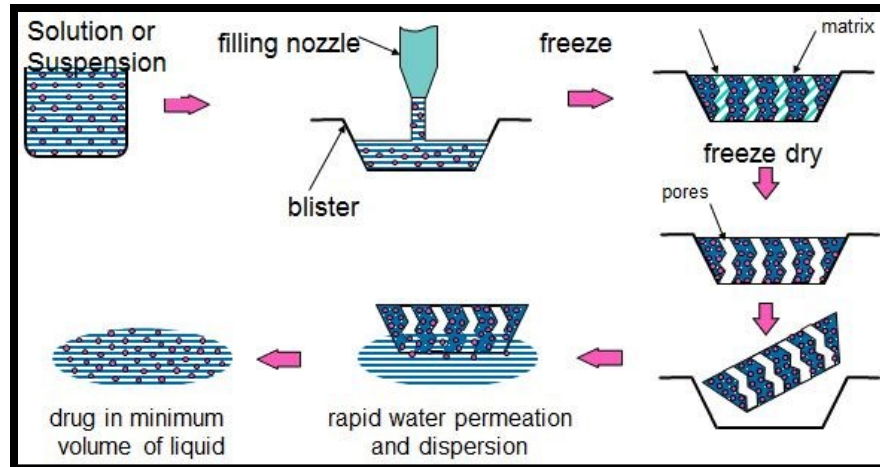
Figure 4-2: Schematic steps of Zydis Technology.

4.3.2 OraSolv Technology

This technology was the first ODTs dosage form that manufactured by CIMA's Lab Inc., [51]. The API is masked by disintegrating agent. The disintegration action is based on the use of effervescent agent that activated once it placed in the mouth. Some of the mainly effervescent agents that acid source (citric, tartaric, malic, fumeric, adipic and succinics) and a carbonate source (sodium bicarbonate, sodium carbonate, potassium bicarbonate and potassium carbonate, magnesium carbonate). They are used in 20 to 25% of the total weight of the tablet. The manufacturing requires controlled environment from humidity and protection by using moisture impermeable blisters [42].

4.3.3 DuraSolve Technology

It was developed by CIMA's Lab Inc., to provide for packaging in conventional blisters or bottles. Fillers and lubricants are the main component to produce the formulation. The particle sizes of fillers (e.g. dextrose, mannitol, sorbitol, lactose, and

sucrose) are preferable to be 20 to 65μm. The lubricants blending time can be increased to 10–25 minutes or longer. The yield tablets have a rapid disintegration and dissolution times (less than 60 seconds) with higher mechanical strength. It is produced by conventional direct compression, and therefore it is very cost-effective [23, 52].

Some of the disadvantages used by this technology are not suitable for large doses of active ingredients because the formulation is subjected to high pressure during compaction. The coating powder blend of the drug may tend to crack during compaction, which exposing the bitter taste of drugs. Thus, this technology is suitable for tablets having low amount of active ingredients [47].

4.3.4 Flash Dose Technology

This technology was patented by Fuisz, and also known as Shear form. It utilizes a unique spinning mechanism to produce a floss-like crystalline structure as cotton candy technique [53]. The feed stock that prepared with a sugar carrier will be exposed to flash heat processing. The crystalline sugar will be incorporated the active ingredient and be compressed into a tablet. The yield product will have very high surface area for dissolution. It will be highly porous in nature and offer very pleasant mouth feel due to rapid solubilization of sugars in presence of saliva which make that tablet disperses and dissolves quickly once placed on the tongue [42, 54].

4.3.5 Flash Tab Technology

This technology patented by Prographarm laboratories. It produced the ODTs by using a combination of disintegrating agent and a swelling agent that coated the API particles and allow the tablet to disintegrate in the mouth less than a minute [55].

4.3.6 Wow Tab Technology

This technology uses that same technique that used in the tablet manufacturing by using conventional granulation. A combination of low moldability saccharides (e.g. lactose, mannitol, glucose, sucrose, and xylitol) and high moldability (e.g. maltose, sorbitol, and oligosaccharides) was utilized to produce fast dissolving tablets. Both saccharides will be granulated and use as a binder in order to achieve the desired properties of suitable hardness and quick disintegration in the mouth [46].

4.3.7 OraQuick Technology

This technology patented by KV Pharmaceuticals Company. It utilizes a patented taste mask to produce ODTs. It is suitable for heat sensitive drugs since low heat will release during process. The final product has a matrix surrounds and protects the drug powder in microencapsulated particle which make it more pliable. Therefore, this technique produce an ODTs with good taste masking and quick dissolution in matter of seconds [6, 42].

4.3.8 Quick-Dis Technology

This technology was invented and patented by Lavipharm Laboratories Inc. It is a novel intraoral drug delivery system to manufacture the ODTs that constituent of a thin, flexible and quick dissolving film with 2mm of thickness placed on the top of the tongue to disintegrate instantly (5 to 10 seconds) and release the active ingredient for system absorption. According to the release profile, this technology produced a tablet that released 50% of the active ingredient within 30 seconds and 95% in one minute. The final product can be packaged by unit-dose pouches to multiple-dose blister packages [4, 56].

4.3.9 Ora-Dis Technology

This technology prepared by utilizing the conventional direction compression method. The orally disintegrating tablet manufacturing by this technology has many advantages compared with other technologies in the market. The ODT has a rapid disintegration time in the mouth between 15 to 30 seconds. The formulation produced a hard tablets with no fragile which make them easy to handle. There is no specific packing required, which can be packaged in push –through blisters. The final product provide smooth pleasant mouth feel with acceptable taste since masking agents and flavor are incorporated in the formulation. All the materials used in the formulation meets USP and EP standards. This technology is very cost effective since it uses the conventional manufacturing equipment for direction compression [4].

4.3.10 Melt Ease Technology

This technology was developed by nutrition formulators allow the ODTs dissolution in less than five seconds for an average tablet load of 400 mg. This technology has helped to ensure compliance and increase sales in two essential markets, children and the elderly for many nutritional supplements at a very marginal development cost effect in specific formulations, including taste masking and sustained release on certain ingredients [4, 57].

4.3.11 Ceform Technology

This technology uses microspheres that containing the active ingredients during the preparation [27]. The pharmaceutical active ingredient can be used alone on in

combination with other excipients to place into a precision engineered rapidly spinning machine. The dry drug blend will spin at high speed to form a sphere, without affecting the drug stability by controlling the temperature. The microspheres will be formed and compressed into tablets.

A unique environment will be created during the preparation since both the API and other excipients processed simultaneously. This environment allows the materials to be incorporated into the microspheres and alter the characteristics of the drug to enhance the solubility and stability of the formulation [58].

4.3.12 Lyoc Technology

The ODTs produced by this method are very porous form produced by lyophilization of oil-in-water emulsion that placed directly in the blister alveolus. This method involves freezing a thickened emulsion that contains the API as coated microparticles. This unique technique allows formulating an ODT with high dose of the drug that is disintegrate instantly [33].

4.3.13 Pharmburst Technology

It was patented by SPI Pharma. The tablet formulation used by this technique involves a dry blend of an API, flavors, and lubricant followed by direct compression to produce tablets which dissolve within 30-40 seconds. Tablets manufactured by this methodology have sufficient strength can be packed in blister packs and bottles [59].

4.3.14 Forsta Technology

This technology was patented by Akina based on the compression method. It has unique properties by having fast disintegration time and high mechanical strength. This concept of technology is to compress highly plastic granules at low pressures. The highly plastic granules are composed of three components: a plastic material, a water-penetration enhancer and a wet binder, each component plays an important role to produce tablets with higher strength and faster disintegration time. Based on the size of tablet, the disintegration time in the mouth of Forsta technology can be 5 to 40 seconds. It is cost effective technology since it uses the same conventional tablet machines. It produced by simple processing since it used one step of we granulation processing. The yield product will have a strong mechanical property (friability <1%). Many tablets can be packaged in one bottle (multi-tablet packaging) [60]. Figure 4-3 shows the processing step for making highly plastic granules and fast melting tablet.
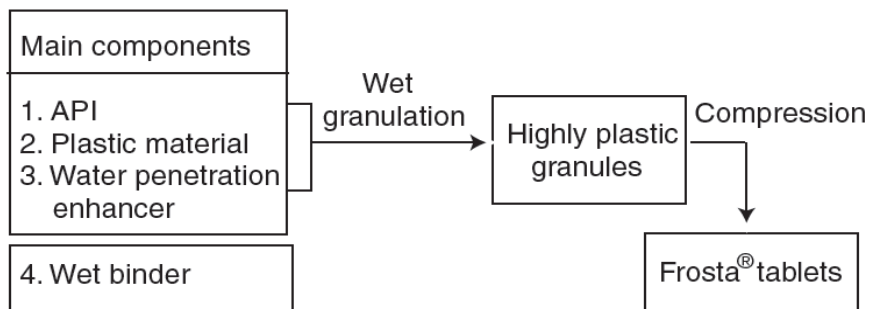
Figure 4-3: A simplified schematic steps of Forsta Technology

4.3.15 Advtab Technology

This technology was patented by Kyowa Hakko Kogyo (Tokyo, Japan). It uses the lubrication to dispense onto each tablet by using a spray during the production

process. The formulation produced is 10 to 30 times less hydrophobic lubricant and 30% to 40% stronger than conventional tablets. Therefore, the final products are hard and durable as well as allow a quick liquid entry upon the contact with the saliva. This technology gives an opportunity to handle high drug content and coated drug particles. It is also not require special packaging, thus can be packaged in both standard bottles and push-through blisters [46].

4.3.16 Nanocrystal Technology

This technology was developed recently and involves reduction in the particle size of the drug to the nano-size by wet milling technique. It is mainly advantageous for poor water soluble drugs and also for wide range of doses (up to 200 mg of drug per unit) [43, 61]. Water-soluble GRAS (Generally Regarded as Safe) ingredients are incorporated with the nanocrystal colloidal dispersions of API and filled into the blister for lyophilization to yield a wafer that has a nanoparticles (<2 microns) in the form of a rapidly disintegrating tablet matrix and highly dissolvable in seconds once it placed upon the mouth. This technology is very suitable when working with highly potent or hazardous materials in order to avoid manufacturing operations (e.g., granulation, blending, and tableting) that generate large quantities of aerosolized powder and present much higher risk of exposure [4, 42, 54].

4.4 Other Technologies for Fast Dissolving

Fast dissolving film is a new type of formulation that developed recently to deliver a very convenient means of taking medications. Water soluble polymer (e.g.,

pullulan, hydroxypropyl methylcellulose, carboxy methylcellulose, hydroxyl ethylcellulose, hydroxyl propylcellulose, polyvinyl pyrrolidone, polyvinyl alcohol or sodium alginate, etc) mixed with is with the drug and other taste making ingredients to make a solution that undergo to solvent evaporation to form a film. The yield film melts or dissolves instantly to release the active ingredient once it placed in the mouth [33].

4.5 Technologies for Fast Dissolving Film Preparation

4.5.1 Soluleaves Technology

The film produced by this technology is able to release the active ingredient once it placed on the mouth and come in contact with saliva. It is designed specifically to help pediatric and geriatric patients who may have difficulty swallowing conventional tablets. The product will adhere to the mucous membrane inside the mouth to produce a slow release of the drug approximately in 15 minutes [62].

4.5.2 Foambucrst Technology

It is a patented technology that made up of foamed film for capsules. A gas is blown into the film during the manufacturing allowing a yield film that has honeycombed structure. The void in the film can be filled with pharmaceutical ingredients to provide a specific taste burst feature to deliver the active ingredient. The structure of the honeycombed provide the capsules to dissolve instantly and causing a melt-in-the mouth sensation [62].

4.5.3 XGel Technology

This film technology was developed by BioProgress to enhance the product stability. The film can be colored and printed during manufacturing process for branding and coding. This technology allows the pharmaceutical industry use very widely to enhance product identification. It is also developed to use for ingestible applications such as cosmetic, ostomy pouches, sanitary and healthcare devices [23].

4.5.4 Wafer Tab Technology

It is a unique, innovative, and highly stable edible film dose form. It is drug delivery system that incorporates pharmaceutical active ingredients into ingestible film strip. It provides a very rapid dissolution time once the strip comes in contact with saliva. The film strip can be flavored to improve taste masking and prepared in a variety of shapes and sizes. The technology is suitable for drugs that need to be released quickly to provide pharmaceutical actions and convenient for patients who are suffering from swallowing difficulty [23].

Chapter 5

Superdisintegrants

5.1 Introduction

These are agents utilize in the tablet formulation in order to break up the compacted mass into the primary particles and facilitate the dissolution and release of the active ingredients once they placed into a fluid environment. They promote moisture penetration and dispersion to the tablet matrix [34]. Orally disintegrating tablets are formulated and achieved by the using of a suitable superdisintergrant. They are newer substances that characteristics with greater disintegrating efficiency and mechanical strength at lower concentrations. They provide rapid disintegration due to combined effect of swelling and water absorption by the formulation. The swelling effect will increase the wetted surface of the carrier which promotes the wettability and dispersibility of the system and lead to enhancing the disintegration and dissolution. They also improved compressibility and compatibility without negative impact on the mechanical strength of formulations containing high-dose drugs [63]. The swelling pressure and isotropic swelling of the superdisintegrants particles will create stress concentrated areas where a gradient of mechanical properties will exist which eventually

allow the structure of the tablet to break apart.   Figure 5-1 shows the steps of the disintegration mechanism [64].
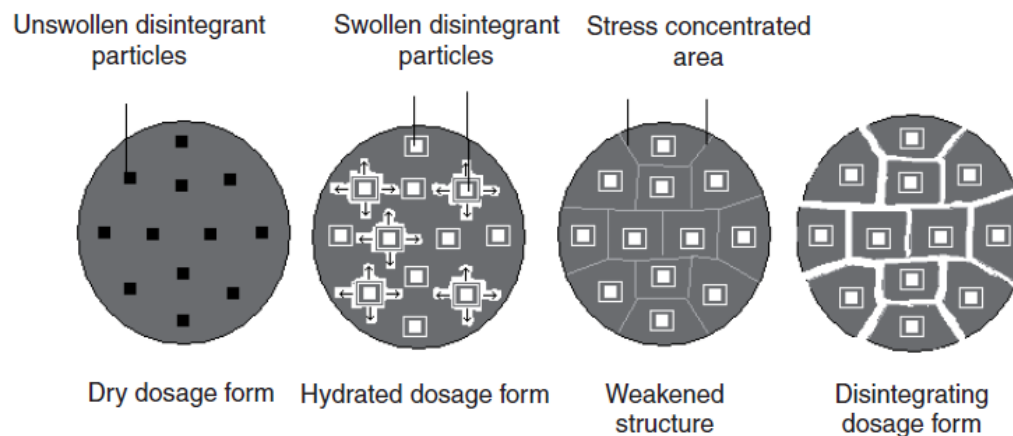
Figure 5-1: Schematic Disintegration mechanism of steps of superdisintegrants materials.

5.2 Characteristics of an Ideal Superdisintegrants [34, 64, 65]

- Poor solubility.

- Poor gel formation.

- Good hydration capacity.

- Good molding and flow properties.

- No tendency to form complexes with the drugs.

- Pleasant mouth feel.

- Compatible with the other excipients and have desirable tableting properties.

5.3 Factors Consideration for Superdisintegrants Selection

- It should produce mouth dissolving when tablet meets saliva in the mouth.

- Enough compatibility to yield tablets with less friability.

- It should have a small particle size with good mouth feel to the patient in order to achieve patient compliance.

- It should have good flow since it improve the flowability of the total blend.

5.4 Methods of incorporating superdisintegrants into tablets [34, 66]

- **Internal Addition (Intragranular)**: Superdisintegrants should be incorporated within granules prior to wetting the powder mixtures with the fluid granulation.

- **External Addition (Extragranular)**: Superdisintegrants should be incorporated to the sized granulation with mixing prior to compression.

- **Partly Internal and External**: In this method, superdisintegrants can be divided and incorporated internally and externally. This can help to produce a rapid disruption of the tablet and provide additional erosion of the granules of the original powder particles.

5.5 Mechanisms of Superdisintegrants [26, 34, 67, 68]

5.5.1 Swelling

It is the most widely mechanism that used in the ODTs preparation. The adhesiveness of other ingredients that made up the tablet will overcome and causing the tablet to fall apart once the tablet gets in contact with water. Figure 5-2 is illustrating the swelling mechanism.
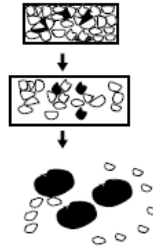
Figure 5-2:   Liquid is drawn up into the pores and rupture the inter-particulate bonds
causing the table to break apart.

5.5.2 Porosity and capillary action (wicking)

The medium of fluid will penetrate the tablet and replaces the air adsorbed on the

particles. The water uptake depends on hydrophilicity of the drug and excipient as well

as tableting conditions. The maintenance of porous structure and low interfacial tension

towards aqueous fluid is essential to create a hydrophilic network around the drug

particles. Figure 5-3 is illustrating the repulsion mechanism.
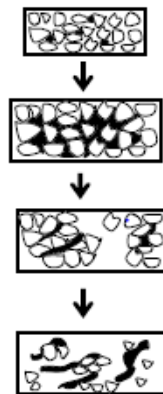
Figure 5-3:   Water is pulled by superdisintegrants causing the tablet particles to well
and volume increases to break the tablet apart.

5.5.3 Particle Repulsive Forces

This mechanism was proposed by Guyot-Hermann based on the observation of non-swellable particles that cause disintegration of tablets. The electric repulsive forces between particles induce the mechanism of disintegration when the tablets come in contact with the fluid. Some researchers consider repulsion is secondary to wicking. Figure 5-4 is illustrating the repulsion mechanism.
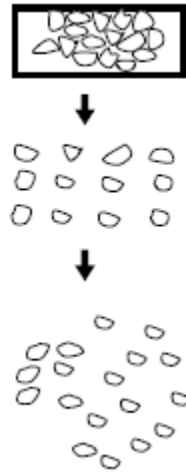
Figure 5-4:   Water is drawn into pores and particles repel each other because of resulting electrical force.

5.5.4 Deformation

In this mechanism, the disintegrated particles will get deformed and distorted during tablet compression. Theses particle will return to their normal shape upon wetting with the aqueous media. Therefore, the size increase of the deformed particle will allow the tablet to break apart. Figure 5-5 illustrates the deformation mechanism in tablet disintegration.
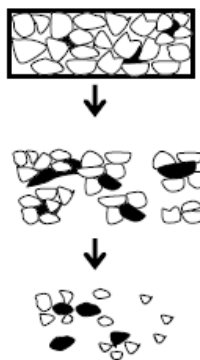
Figure 5-5: Particles swell to pre-compression size and break up matrix.

5.5.5 Heat of Wetting (Air Expansion)

In this mechanism, superdisintegrants with exothermic properties will create a localized stress when they get wet due to the capillary air expansion and tablet will disintegrate.

5.5.6 Acid-Base Reaction (Gas Release)

In this mechanism, the interaction between acids (e.g. tartaric acid and citric acid) and bases (e.g. kali metal carbonates or bicarbonates) in the presence of water will allow the tablet to disintegrate very rapidly due to the liberation of gas (e.g. CO_2). This mechanism helps to enhance the dissolution of the drug as well as improve taste masking. Strict measures are required during tablet preparation since superdisintegrants are highly sensitive in the presence of humidity and temperature. The effervescent blend can be incorporated immediately prior to compression or divided into two separate fraction of formulation.

5.5.7 Enzymatic reaction

Human body contains some enzymes that can act as disintegrants. These enzymes help in disintegration due to pressure exerted in the outer direction. Also the accelerated absorption of water leads to a massive increase in the volume of granules to promote tablet disintegration. Table 5.1 shows some example of disintegrating enzymes along with the binders against which these are active.

Table 5.1: Some examples of enzymes as disintegrating agents

Enzyme	Binder
Amylase	Starch
Protease	Gelatin
Cellulase	Cellulase and it derivatives
Invertase	Sucrose

5.6 Synthetic Superdisintegrants

They are often utilized in the ODTs formulations to improve the tablet disintegration thereby increasing the rate of drug dissolution. The most widely used synthetic superdisintegrants are illustrated below.

5.6.1 Cross-linked polyvinyl Pyrrolidone (Crospovidone)

This substance characterize by high cross-link density allow the tablet to swell very rapidly in aqueous medium by the use of both mechanisms swelling and wicking. The particles of crospovidone are found to be granular and highly porous that facilitates wicking of liquid into the tablet and generates instant disintegration. The larger particles of crospovidone, the faster disintegration time [69]. The unique particle morphology allows the crospovidone to be highly compressible material. It can be used as a solubility

enhancer in the formulation. There are two particle sizes available in the form of Polyplasdone XL and Polyplasdone XL-10 as crospovidone.

5.6.2 Croscarmellose Sodium (Primellose®)

It is an internally cross-linked polymer of carboxymethylcellulose sodium. The degree of cross-linking and substitution are the important factors in determining the effectiveness of this material as superdisintergrant. The particle size is the key factor of this substance. It has high swelling capacity and fibrous structure that make it perfect superdisintergrant. It can be incorporated in the tablet formulation by both direction compression and wet-granulation methods. For wet-granulation method, it should be divided and added in both stages wet and dry (intra- and extra-granularly) in order to achieve the optimal disintegration effect [70].

5.6.3 Sodium Starch Glycolate (Primojel® and Explotab®)

It is a sodium salt of a carboxymethyl ether of starch. The selection of the type of starch is a key factor to determine the effectiveness of this material. The cross-linking effect reduces both the water soluble fraction of the polymer and the viscosity of dispersion in water. The natural pre-dried starch well to the extent of 10 to 20 % whereas the modified starch increases in volume by 200 to 300 % in water. It produced uniform disintegrating effect by the rapid absorption of water that causes an enormous increase in volume of granules. The large hydrophilic carboxymethyl groups disrupt the hydrogen bonding within the polymer structure which allows water to penetrate the molecule and the polymer becomes cold water soluble [71].

Chapter 6

Quality Control of Tablets

6.1 Preformulation Studies to Evaluate Powder Mixture

These studies pertain to pharmaceutical and analytical investigations that are necessary for proceeding and supporting formulation development efforts of the dosage form of the drug substance. They provide basic knowledge necessary to develop appropriate formulation for toxicological use. They aid in collecting information needed to describe the nature of the drug substance and provide a frame work for the drug combination with pharmaceutical excipients in the dosage form. Therefore, the following preformulation studies were performed while developing orally disintegrating mini-tablets (ODMTs) of Metoclopramide Hydrochloride.

6.1.1 Angle of Repose

The friction forces in a loose powder can be measured by the angle of repose. It is an indication of the flow properties of the powder. It is defined as the maximum angle possible between the surface of the pile of powder and the horizontal plane [26]. The angle of repose was determined according to a recommended procedure described in USP 36. The base should be free of vibration. The peak of the cone may be misshaped by the

strength of the powder flowing from the funnel. Therefore, the height of the funnel should be maintained approximately 2-4 cm from the top of the powder pile as it is being formed in order to minimize the impact of the falling powder on the tip of the cone [72]. The angle of repose was then calculated according to the USP by measuring the height and the base of the heap of powder formed and using equation 6.1 as following:

$$\mathbf{tan(\alpha)} = \frac{\text{height}}{0.5 \times \text{base}}$$ (Equation 6.1)

Equation 6.2 helps to determine and angle of repose by rearranging Equation 6.1:

$$(\mathbf{\alpha}) = \mathbf{tan^{-1}} \times \frac{\text{height}}{0.5 \times \text{base}}$$ (Equation 6.2)

Where: α represents the angle of repose, the height in cm, and the radius/base in cm.

Table 6.1 describes the relationship between the angle of repose and the powder flow property. Powder mixtures with an angle of repose greater than 50 are rarely acceptable for the manufacturing process [73].

Table 6.1: Flow properties and corresponding angles of repose [72, 74]

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

6.1.2 Loose Bulk Density (LBD)

This is the ratio of the total mass of powder to the bulk volume of powder [26]. Accurately weigh a portion of powder mixture (40 g) and transfer it to a 100 ml graduated cylinder. The mixture was carefully leveled without compacting, and read as

the unsettled apparent volume (V_o) [24]. Loose bulk density can be calculated based on equation 6.3 and expressed in g/ml:

$$\textbf{Loose Bulk Density } (\boldsymbol{\rho_{bulk}}) = \frac{\textbf{mass of powder}}{\textbf{unsettled volume } V_o} \qquad \textbf{(Equation 6.3)}$$

6.1.3 Tapped Bulk Density (TBD)

This is the ratio of total mass of the powder to the tapped volume of the powder [26]. Accurately weigh some quantity of powder mixture (40 g) and transfer it to a 100 ml graduated cylinder. The cylinder containing the sample was manually tapped. There is a minimal number to taps required by the USP (500) and a reasonable number seen by the equilibrium at the final volume. The final tapped volume (V_f) was then measured to the nearest graduated units. Tapped bulk density can be calculated based on equation 6.4 and expressed in g/ml:

$$\textbf{Tapped Bulk Density } (\boldsymbol{\rho_{tapped}}) = \frac{\textbf{mass of powder}}{\textbf{final tapped volume } V_f} \qquad \text{(Equation 6.4)}$$

6.1.4 Compressibility Index (Carr's Index)

Equation 6.5 describes the calculation of the Compressibility Index of the powder mixture by using bulk density and tapped density. It measures the powder flowability and is expressed in percentage [24]:

$$\textbf{Compressibility Index } (\%) = \textbf{100} \times \left[\frac{(\boldsymbol{\rho_{tapped}} - \boldsymbol{\rho_{bulk}})}{\boldsymbol{\rho_{tapped}}} \right] \qquad \text{(Equation 6.5)}$$

6.1.5 Hausner Ratio

The Hausner ratio is a number that is correlated to the flowability of a powder or granular material [24]. It is an indirect index to measure the ease of powder flow [26]. Equation 6.6 describes the calculation of Hausner Ratio.

$$\text{Hausner Ratio} = \frac{\rho_{tapped}}{\rho_{bulk}} \qquad \text{(Equation 6.6)}$$

The compressibility index and Hausner ratio are closely related, simple, fast and popular methods for predicting powder characteristics. They indirectly measure bulk density, particle size, shape, surface area, moisture content, and cohesiveness of materials [72]. Table 6.2 describes the relationship between Compressibility Index, Hausner Ratio, and powder flow property as an accepted scale for flowability.

Table 6.2: Scale of Flowability [72]

Compressibility Index (%)	Flow Character	Hausner 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	>1.6

6.2 Pharmacopeial Evaluation Parameters of Tablets Dosage form

6.2.1 Weight Variation Test

Ten (10) tablets were individually and accurately weighed. According to the United States Pharmacopeia and National Formulary (USP 36-NF 31) in order to make analysis of wieght variation of Uncoated or Film-Coated Tablets [75]. The content, expressed as percentage of label claim, was calculated for each tablet from the weight of

the individual tablet and the result of the Assay. Equation 6.7 describes the calculation of the percentage of acceptance value of weight variation [7] and Table 6.3 shows the acceptable criteria for weight variation [76]:

$$\% \textbf{ Weight Variation} = \frac{\textbf{(individula weight}-\textbf{average weight)}}{\textbf{average weight}} \times \textbf{100} \quad \text{(Equation 6.7)}$$

Table 6.3: describes the tolerance of weight variation for the tablet dosage form.

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

6.2.2 Tablet Dimensions

The tablet's dimensions are a very important factor in their manufacture. It helps to determine the targeted size for the tablet in order to make it easy to swallow and handle by the patients [7, 77]. The diameter and thickness were measured by using ten (10) tablets which were selected randomly for analysis, and the average values were calculated.

6.2.3 Friability Test

The tablet friability test determination was achieved accodring to the United States Pharmacopeia and National Formulary (USP 36-NF 31). Figure 1 illustrates the Tablet Friability Apparatus according to the USP. It provides guidelines for the friability determination of compressed, uncoated tablets. Based on the test procedure described in the USP, it can be applicable to most compressed tablets. This test can be used as a supplement to other physical strength measurements, such as tablet breaking force. The

USP 36 recommends the total tablet sample should be taken corresponding as near as possible to 6.5 g for tablets with a unit weight equal to or less than 650 mg. On the other hand, for tablets with a unit weight of more than 650 mg, the sample of 10 whole tablets should be taken. The tablets should be carefully dedusted prior to testing. Accurately the tablet samples were weighed (recorded as initial weight), and placed in the drum. The drum was rotated up to 100 revolutions at 25rpm for 4 minutes [24, 78, 79]. After that time lapse, any loose dust was removed from the table samples by using a brush, and accurately reweighed (recorded as final weight). Equation 5.8 describes the calculation of friability percentage [7]:

$$\textbf{Friability } (\%) = \frac{(\textbf{weight}_{\textbf{initial}} - \textbf{weight}_{\textbf{final}})}{\textbf{weight}_{\textbf{inital}}} \times \textbf{100} \qquad \text{(Equation 6.8)}$$

If obviously cracked, cleaved, or broken tablets were present in the tablet sample after tumbling, the sample fails the test. If the results are difficult to interpret or if the weight loss is greater than the targeted value, the test should be repeated twice and the mean of the three tests determined. Figure 6-1 illustrates the friability apparatus according to USP 36. The maximum mean weight loss from the three samples is not more than 1.0% which is considered acceptable for most products [80].
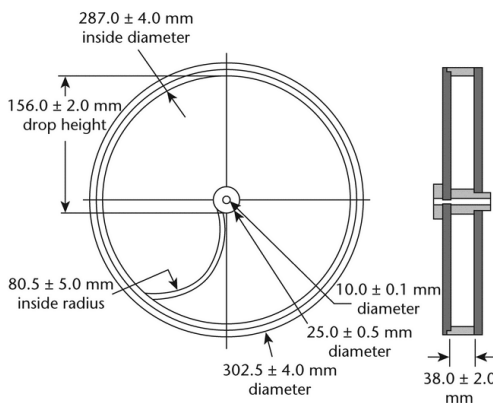
Figure 6-1: Tablet Friability Apparatus according to the USP 36-NF 31[80]

6.2.4 Tablet Breaking Force (Hardness) Test

The breaking force of tablets demonstrates the ability of a tablet to withstand the rigors of handling and transportation experienced in the manufacturing plant, in the drug distribution system, and in the field at the hands of the end users (patients/consumers). During the manufacturing processes such as coating, packaging, and printing can produce significant stresses for the tablet. Therefore, the mechanical strength of tablets is a significant factor that must be routinely measured. Modern breaking force testers are commonly adjusted in kilopounds or newtons. The relationship between these units of force can be converted as follows 1 kilopound (kp) = 1 kilogram-force (kgf) = 9.80 N. A minimum of 6 tablet samples should be tested in order to achieve appropriate statistical precision for the determination of an average breaking force. Ten (10) tablets were randomly picked and the hardness of the tablets was determined [81].

6.2.5 Simulated Wetting Time Test

The simulated wetting time test for the ODT was developed through experimentation. It is a measurement of liquid uptake. One of the methods suggested utilizes Whatman Filter Paper. The filter paper was placed in each well of a Corning 12-well polystyrene microplate (22 mm in diameter). Based on tablet size (Table 6.4), a recommended volume of 0.1% (w/w) Sensient Blue #1 dye solution was then added into each well in different amounts. Then, the ODT was transferred carefully and placed on the surface of the wet paper disk in each well using a pair of forceps as illustrating on Figure 6-2 and finally the total wetting time was measured [82]. The uptake of water started from the lower surface of the tablet. The time required for the dye solution to

diffuse through the tablet to reach the center of the upper surface of the tablet and completely cover the surface was defined as the wetting time.

Table 6.4: Optimum volume of the blue dye solution for a given tablet size.

Recommended volume of dye solution (mL)	Tablet size (mg)
0.75	<49
1.0	50-99
1.25	100-379
1.5	380-800
1.75	>800
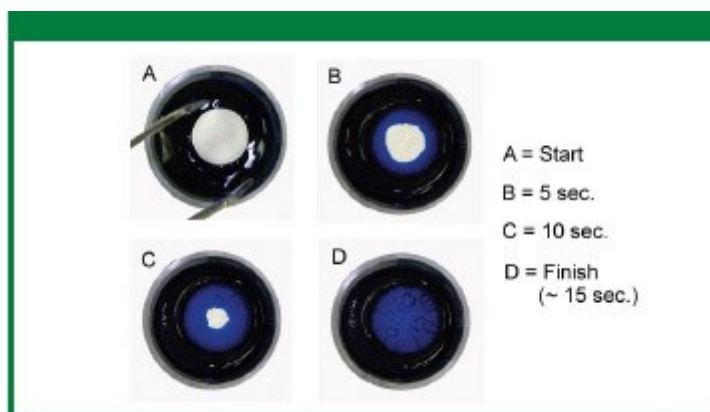
Figure 6-2:   Simulated wetting test for evaluating the disintegration time of oral disintegrating tablets [83]

Another method was further developed by second research group [83] which established a second method for Wetting Time.   The new method simulates the physiological conditions found on the wet tongue surface, since the mechanical stress, induced by the human tongue was intentionally disregarded. The method takes tablet size into consideration; therefore, it was modified with regard to the small size of the ODTs. The Whatman filter paper disc (5 mm in diameter) was placed in each well of a 96-well plate and 20 µl of a 0.1% (w/w) Brilliant Blue 85 E 133 solution was added. The blue

dye solution was utilized to allow suitable visual end-point detection. And finally, the time required for the blue dye solution to wet the tablet completely was determined [83].

A unique method was developed by a graduate student from University of Toledo. A small dry sponge (1 cm x 1 cm), and 1 mL of room temperature deionized water were used to simulate the saliva production in one minute and the surface of the tongue [84]. This unique method was developed by us (University of Toledo, OH) and will be recommended to the USP for consideration [73]. The wetting time test was performed by adding Brilliant Blue 85 E 133 solution to the distilled water to make a blue dye solution, which will enable suitable visual end-point detection for water uptake.

6.2.6 In-vitro Disintegration Time Test

The in-vitro disintegration time test is a significant characteristic required for orally disintegrating tablets. The disintegration time for ODT dosage forms must be within a minute. Figure 6-3 illustrate the disintegration apparatus that used to determine disintegration time according to USP 36 [78]. One tablet should be placed in each of the six tubes of the disintegration basket apparatus, one disc was added to each tube, and was measured at 37±2°C using 900ml of distilled water [85]. The time was measured in seconds for complete disintegration of the tablet with no palpable mass remaining in the apparatus. At the end of the time limit specified in the monograph, lift the basket from the fluid, and observe the tablets. According to the test, all of the tablets must disintegrate completely within one minute. In case if one or two tablets fail to disintegrate completely, the test must be repeated at least on 12 additional tablets. The USP requires at least 16 of the total of 18 tablets that tested are disintegrated [86].

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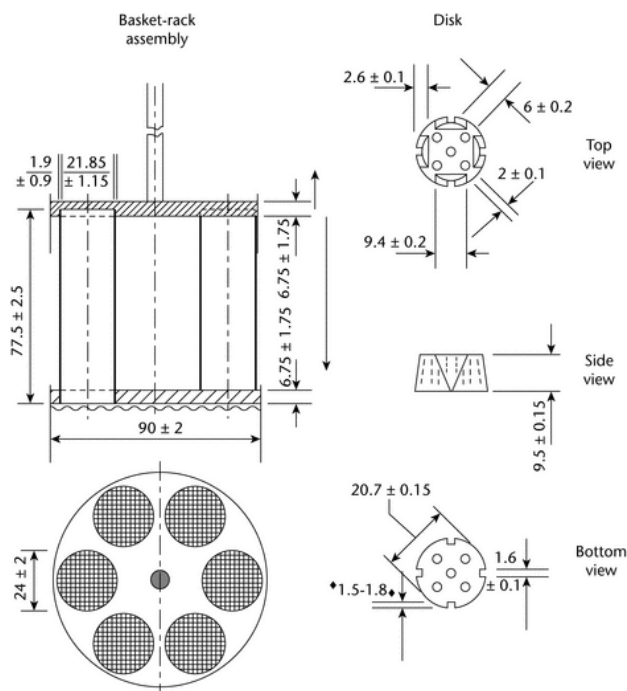
Figure 6-3: Disintegration apparatus (All dimensions are expressed in mm)[86]

6.2.7 In-vitro Dissolution Analysis

The in-vitro dissolution test was carried out using simulated gastric fluid with USP dissolution apparatus II at 50 rpm and 37±0.5 °C temperature [87]. 5 mL was withdrawn at predetermined time interval. Then, the test sample solution was filtered and its absorbance was analyzed using ultraviolet (UV) spectrophotometer at λ_{max} 272 nm in order to determine Metoclopramide Hydrochloride concentration [88].

6.2.8 Accelerated Stability Study

Accelerated stability studies for orally disintegrating tablets were established according the ICH guidelines. ODTs are packed in a suitable packaging and stored under the following conditions: 40 ± 1°C, 50 ± 1°C, and 37 ±1°C. Relative humidity should be

at 75% ± 5%. The tablets were withdrawn after a period of 15 days and analyzed for physical characterization (Visual defects, Hardness, Friability, Disintegration, Dissolution etc.) and drug content. The data obtained is fitted into first order equations to determine the kinetics of degradation. Accelerated stability data are used for plotting graph in order to determine the shelf life at 25°C according to Arrhenius equation [43, 45, 89, 90].

Chapter 7

Development of Metoclopramide HCl Orally Disintegrating Mini-Tablets

7.1 Physicochemical characteristics of Metoclopramide Hydrochloride

Metoclopramide Hydrochloride, the systematic (IUPAC) name known as, 4-amino-5-chloro-N-[2-(diethylamino) ethyl]-2 methoxybenzamide monohydrochloride monohydrate (Fig.7-1)[87]. It has a chemical formula of $C_{14}H_{22}ClN_3O_2 \cdot HCl$ and a molecular weight of 354.27 g/mol. According to the USP , Metoclopramide Hydrochloride contains not less than 98.0% and not more than 101.0% of metoclopramide hydrochloride ($C_{14}H_{22}ClN_3O_2 \cdot HCl \cdot H_2O$), calculated on the anhydrous basis [91]. Metoclopramide Hydrochloride is a white, crystalline powder, odorless substance, very soluble in water and freely soluble in alcohol, and sparingly soluble in methylene chloride.
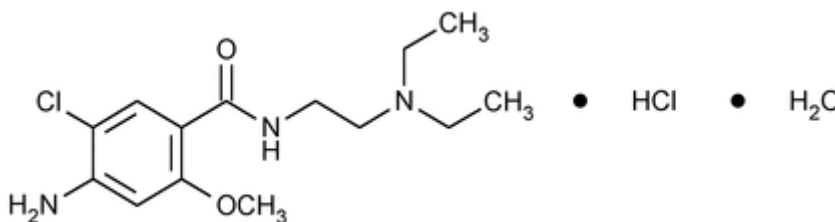
Figure 7-1:   Structural formula of USP Metoclopramide Hydrochloride RS, (USP 37-NF 32) $C_{14}H_{22}ClN_3O_2 \cdot HCl \cdot H_2O$

It has a very rapid absorption in gastrointestinal tract (GIT) after oral administration [92-94]. It has a relatively short biological half-life (5 ± 1 h) and is usually administered in orally 10–15 mg four times daily, as immediate release tablets, which results in extrapyramidal symptoms as side effects from the from the frequent administration [95]. Metoclopramide clinically has a potent dopamine (D2) receptor antagonist effect in the chemoreceptor trigger zone (CTZ) in the central nervous system (CNS) with prokinetic and antiemetic properties that will prevent the nausea and vomiting triggered by most stimuli [93]. It helps to stimulate the motility of the upper gastrointestinal (GI) tract and possessing para-sympathomimetic activity.

It has poor bioavailability due to extensive first pass metabolism when it given by conventional dosage forms such as tablet and solution. The absolute oral bioavailability of metoclopramide is 80 ±15.5% and peak plasma concentrations occur approximately 1–2 h after ingesting a single oral dose. It metabolized hepatically to produce glucuronide and sulphate through the cytochrome P450 CYP2D6 pathway [94]. Metoclopramide is used widely for the treatment of gastrointestinal (GI) motility disorders because of its prokinetic properties.

Therapeutic indications are gastroparesis or ileus, gastro-esophageal reflux disease, dyspepsia, nausea and vomiting during migraine or cancer therapy. Its therapeutic range is from 1 mg for pediatric use to 40 mg for adults. The total daily dosage should not exceed 500μg/kg [93, 96, 97]. The usual oral dosage of metoclopramide in adults is 10 mg, 20 to 30 minutes before meals, and at bedtime for 2-9 weeks are prescribed as tablet for the treatment of diabetic gastroparesis. It is a condition that reduces the ability of the stomach to empty its contents. The symptoms of gastroparesis

can be characterized by abdominal distension, hypoglycemia (in people with diabetes), nausea, premature abdominal fullness after meals, weight loss, and vomiting [98, 99]. It is also given 4 times daily (q.d.s.) for short term treatment ($\leq$ 12 weeks) of symptomatic gastro-esophageal reflux disease (GERD). Metoclopramide effects as antiemetic have proven clinically in the treatment of chemotherapy-induced nausea and vomiting [100], which are thought to involve a dopamine D_2 receptor blockade in the central nervous system, specifically in the vomiting centre and the area postrema [98]. Dosage up to 80 mg/day of Metoclopramide can be tolerated; however the incidence of adverse effects can increase above 40 mg. For diagnostic procedures in adults, metoclopramide 20 mg can be given orally 30 minutes before the procedure or parenterally, 10 to 20 mg 5 minutes before examination. The total daily dose in children should not exceed 0.5 mg/kg body weight [101].

7.2 Challenges in Formulating ODTs [7, 102]

7.2.1 Palatability

Most of the orally disintegrating tablets contain unpalatable drugs. There drugs will be in contact with the taste buds of the patients after they disintegrates or disperse in the oral cavity. Therefore, the need for taste mask is very crucial factor to enhance the palatability and improve patient compliance.

7.2.2 Mechanical strength

ODTs are made to be very porous and soft-molded matrices or compressed by tablet machine at low compression force. This result in friable and brittle tablet that is

difficult to handle the transportation and the normal use of patient's daily activities. Therefore, most of manufacturing use specialized peel-off-blister packing that may increase the cost of production. There are few technologies in the market recently have achieved to formulate ODTs that are elegant and sufficient with mechanical strength to be packaged in multi-dose bottles.

7.2.3 Hygroscopicity

Most of the ODTs made from excipients that highly hygroscopic. They will lose the physical integrity under normal conditions of temperature and humidity. Thus, they need to be avoided from humidity and keep in dry place.

7.2.4 Amount of the Drug

The amount of API need to be incorporated into each unit dose of ODT has limited the application of the ODT dosage form for most drugs. For example, in the lyophilization technique there are limited amount for soluble and insoluble drugs that allowed to be used in the preparation of ODT. This parameter is mostly challenging when manufacturing a fast-dissolving oral films or wafers.

7.2.5 Aqueous Solubility

Water soluble drugs may include some of the challenges in the formulation of ODTs. They tend to form eutectic mixtures that produce a freezing-point depression and eventually they lose the supporting structure during the sublimation process because of the formation of a glassy solid that may collapse upon drying. This event can be

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inhibited during the manufacturing by using various matrix-forming excipients. One of the excipient that induces crystallinity is mannitol. It aids to impart rigidity to the amorphous composite.

7.2.6 Size of Tablet (Small vs. Large)

Patients' poor acceptance of, and compliance with, existing delivery regimes, limited market size for drug companies and drug uses, coupled with high cost of disease management are factors that determined the need for non-invasive drug delivery systems [77].

The recommendations would have to consider the requirements for different climate zones to include the medication in the developing countries. The stability of liquid formulations will be affected by high temperatures. Furthermore, high costs for transportation and storage have to be taken into account. Therefore, liquids should be avoided whenever possible and solid dosage forms, which fulfill desired properties for pediatric use, are highly recommended for global use [83].

Orally disintegrating tablets (ODTs) disintegrate in the mouth into small particles in a few seconds [103]. They have a disintegration time of less than sixty seconds; therefore they belong to fast-dissolving drug formulations, like oral lyophilisates and wafers. These formulations should be preferred applicable for children [104]. A published experimental study investigated the acceptability of commercially available orodispersible tablets made from mannitol, crospovidone, and magnesium stearate, and other excipients with 20 mg prednisolone to 12-year-old children with ear, nose and throat disorders. A good acceptance for 96% of the patients was shown [105]. Orally

disintegrating dosage forms are mostly suitable for patients, who sometime find it difficult to swallow traditional tablets and capsules with an 8-oz glass of water. These include the following [77]:

- Patients who have difficulty in swallowing or chewing solid dosage forms such as pediatric and geriatric.

- An eight-year old with allergies who desires a more suitable dosage form than antihistamine syrup.

- Very elderly patients with antidepressant who may not able to swallow a daily dose of the drug.

- Middle-aged women who are treating from breast cancer and undergoing to radiation therapy feel too nauseous to swallow solid dosage forms.

Tablet dosage form was reported to be a better and easier formulation to handle compared to other formulation such as capsules or powders based on a published survey for patients who experienced difficulty in taking medication. Based on previous studies, tablet size plays a major role to determine the degree of ease when taking a tablet. According to published data, it has been reported that the suitable and easiest size of tablet to swallow is 7-8 mm while the easiest size to handle was one larger than 8 mm. Thus, the tablet size that is both easy to take and easy to handle is difficult to achieve [7, 77, 106]. Orally disintegrating tablets (ODTs) can be manufactured by different processes such as lyophilization, moulding and sublimation, using a sugar-floss system or direct compression [33].

The purpose of this study was to develop and design the mini-tablet and the fast-dissolving dosage form approaches to prepare orally disintegrating mini-tablets (ODMTs)

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of Metoclopramide Hydrochloride, using various pharmaceutical compositions to enhance patient compliance mainly for pediatric and geriatric patients. Metoclopramide HCl was formulated into orally disintegrating mini-tablets using the direct compression method because of convenient and cost-effective.

Chapter 8

Materials and Methods

8.1 Materials and Equipment

8.1.1 Metoclopramide Hydrochloride (MTH)

Metoclopramide Hydrochloride (MTH) Monohydrate pure sample was used as the active pharmaceutical ingredient to provide antihistamine properties in the fast dissolving tablet. Metoclopramide Hydrochloride (Lot No. 1203220074) was purchased from Letco Medical Supplies (Decatur, AL).

8.1.2 Superdisintegrants

A sample of Polyplasdone XL[®]: crospovidone was purchased from GAF Chemical Corporation (Wayne, NJ). Primojel[®]: sodium starch glycolate (Lot No. 4AU061OH) was purchased from Chelsea Labs, Inc. (Monroe, NC).

8.1.3 Diluents

Avicel[®]: Microcrystalline Cellulose (MCC, Lot No. 2509, 5522N) was provided from FMC Corporation (Newark, DE). A sample of Treha Trehalose (Lot No. 2F101) was obtained from The Endowment for Medical Research and Cargill (Wayzata, MN).

8.1.4 Lubricants

Talc Powder USP (Lot No. 10151214) was provided from Letco Medical Supplies (Decatur, AL). Magnesium stearate (Lot No. 742748) was purchased from Fisher Scientific (Fair Lawn, NJ)

8.1.5 Dye for Wetting Time Test

Brilliant Blue 85 E 133 (Lot No. SL1127) was obtained from Spectrum Chemical Manufacturing Corporation (New Brunswick, NJ).

8.1.6 Simulated Gastric Fluid without Enzymes

The preparation of simulated gastric fluid without enzyme was prepared according to the USP 37 standard method to be used as a dissolution medium [107]. Hydrochloric acid (lot No. M153KMCP) was purchased from Chempure (Houston, TX) and diluted with deionized water. Sodium chloride was purchased from Sherman Research Laboratories (Toledo, OH) and dissolved in the acidic solution.

8.1.7 Deionized water

Deionized water was supplied by the University of Toledo Health Science Campus deionization system.

8.1.8 Humidity Testing Salts

Sodium chloride, purchased from Sherman Research Laboratories (Toledo, OH), was used to create 75% relative humidity in sealed baby food jar desiccators. Sodium bromide was used (Lot No. Z7435I18) created 60 % relative humidity environment and was purchased from Ruger Chemical Co Inc. (Linden, NJ).

8.1.9 Equipment Used

Table 8.1: Equipment used for ODT formulation and evaluation

No.	Equipment	Model
1	Analytical digital balance	Intelligent Weighing Technology's model PM-300
2	Hardness Tester	Sotax Hardness Tester model HT1 4127.013
3	Friability Test Apparatus	Erweka Model TAP 23644
4	Tablet Punching machine	Manesty Tableting Press, Liverpool No. 2L187
5	Disintegration Apparatus	Erweka model ZT2 27151
6	Dissolution Apparatus	Sotax AT 7Smart Serial No. 62078
7	UV-Spectrophotometer	Agilent G1103A, Serial No. CN22808134

8.2 Excipients Profiles [8, 108]

8.2.1 Microcrystalline Cellulose: Standard grade with large particle size is used for improving the flow in direct compression, the dry phase of wet granulation and dry granulation.

Table 8.2: Excipient profile of microcrystalline cellulose used for ODT formulation

Synonyms	Avicel, cellulose gel, crystalline cellulose, E460, Emocel, Fobrocel, Tabulose, Vivacel.
Functional category	Tablet and capsule diluent, suspending agent, adsorbent, tablet disintegrant.
Applications	As a diluent in tablets (wet granulation and direct compression) and capsule formulation. It also has some lubricant and disintegrant property.
Description	White colored, tasteless crystalline powder composed of porous particles
Solubility	Slightly soluble in 5% w/v sodium hydroxide solution, practically insoluble in water, dilute acids and most organic solvents.
Stability	It is a stable, though hygroscopic material. Storage conditions: The bulk material should be stored in a well-closed container in a cool, dry place.
Incompatibilities	Incompatible with strong oxidizing agents.
Safety	It is generally regarded as a non-toxic and non-irritant material.

8.2.2 Trehalose

Table 8.3: Excipient profile of trehalose used for ODT formulation

Synonyms	Ascend; mycose; natural trehalose; a,a-trehalose; Treha
Functional category	Color adjuvant; flavor enhancer; freeze-drying agent; humectant; stabilizing agent; sweetening agent; tablet diluent; thickening agent
Applications	Used for the lyoprotection of therapeutic proteins, particularly for parenteral administration. Other pharmaceutically relevant applications include use as an excipient for diagnostic assay tablets; for stabilization during the freeze–thaw and lyophilization of liposomes;and for stabilization of blood cells, cosmetics, and monoclonal antibodies. Trehalose may also be used in formulations for topical application.
Description	Occurs as virtually odorless, white or almost white crystals with a sweet taste (approximately 45% of the sweetness of sucrose).
Solubility	Soluble in water; very slightly soluble in ethanol (95%); practically insoluble in ether.
Stability	It is a stable, though hygroscopic material. Storage conditions: The bulk material should be stored in a well-closed container in a cool, dry place.
Incompatibilities	Incompatible with strong oxidizing agents, especially in the presence of heat.
Safety	It is generally regarded as a non-toxic and non-irritant material.

8.2.3 Crospovidone

Table 8.4: Excipient profile of crospovidone used for ODT formulation

Synonyms	Cross-linked povidone, polyplasdone XL, Kollidon CL.
Functional category	Tablet and capsule disintegrant. Crospovidone is a water insoluble synthetic cross-linked homopolymer of N-vinyl-2-pyrrolidone used at 2-5% concentration in tablets.
Applications	As a diluent in tablets (wet granulation and direct compression) and capsule formulation. It also has some lubricant and disintegrant property.
Description	Crospovidone is a white to creamy white, finely divided free flowing, practically tasteless, odorless or nearly odorless hygroscopic powder.
Solubility	Slightly soluble in 5% w/v sodium hydroxide solution, practically insoluble in water, dilute acids and most organic solvents.
Stability	Crospovidone is stable. However, since it is hygroscopic, it should be stored in an air-tight container in a cool and dry place.
Incompatibilities	Crospovidone is compatible with most organic and inorganic pharmaceutical ingredients. When exposed to high water level crospovidone may form molecular adducts with some materials.
Safety	Crospovidone used in oral formulation is generally regarded as nontoxic and non-irritant material.

8.2.4 Sodium Starch Glycolate (SSG)

Table 8.5: Excipient profile of SSG used for ODT formulation

Synonyms	Carboxymethyl starch, Explotab, Primojel.
Functional category	Tablet and capsule disintegrant.
Applications	As a disintegrant in tablet (wet granulation and direct compression) and capsule formulation in 2-8% concentration.
Description	White to off-white, odourless, tasteless, free-flowing powder.
Solubility	Practically insoluble in water; sparingly soluble in ethanol (95%). In water it swells up to 300 times its volume.
Stability	It is a stable material. It should be stored in a well closed container to protect from wide variations in humidity and temperature that may cause cracking.
Incompatibilities	Incompatible with ascorbic acid.
Safety	It is generally regarded as a non-toxic and non-irritant material. However, oral ingestion of large quantities may be harmful.

8.2.5 Talc

Table 8.6: Excipient profile of talc used for ODT formulation

Synonyms	Magsil Osmanthus, Magsil Star, Purtalc, steatite
Functional category	Glidant, tablet and capsule lubricant, anti-cracking agent.
Applications	It is used as a lubricant in solid dosage forms (1-10 %), in topical preparations as dusting powder (90-99 %).
Description	It is a very fine, white to grayish-white colored, odorless, impalpable, unctuous powder. It adheres to the skin, is soft to touch, and free from grittiness.
Solubility	Practically insoluble in dilute acids and alkalies, organic solvents, and water.
Stability	Talc is a stable material. Storage conditions: It should be stored in a well-closed container in a cool, dry, place.
Incompatibilities	Incompatible with quaternary ammonium compounds.
Safety	Following oral ingestion talc is not absorbed systemically and may thus be regarded as an essentially nontoxic material. Intranasal or IV abuse of products containing talc can cause granulomas in body tissues, particularly the lungs.

8.2.6 Magnesium Stearate [108]

Table 8.7: Excipient profile of Magnesium stearate used for ODT formulation

Synonyms	Dibasic magnesium stearate; magnesium distearate; magnesia stearas; magnesium octadecanoate; octadecanoic acid, magnesium salt; stearic acid, magnesium salt; Synpro 90.
Functional category	Tablet and capsule lubricant.
Applications	Used in cosmetics, foods, and pharmaceutical formulations. It is primarily used as a lubricant in capsule and tablet manufacture at concentrations between 0.25% and 5.0% w/w. It is also used in barrier creams.
Description	Very fine, light white, precipitated or milled, impalpable powder of low bulk density, having a faint odor of stearic acid and a characteristic taste. The powder is greasy to the touch and readily adheres to the skin.
Solubility	Practically insoluble in ethanol, ethanol (95%), ether and water; slightly soluble in warm benzene and warm ethanol (95%).
Stability	Magnesium stearate is stable and should be stored in well closed container in a cool, dry place.
Incompatibilities	Incompatible with strong acids, alkalis, and iron salts. Avoid mixing with strong oxidizing materials. Magnesium stearate cannot be used in products containing aspirin, some vitamins, and most alkaloidal salts.
Safety	Used as a pharmaceutical excipient and is generally regarded as being nontoxic following oral administration. However, oral consumption of large quantities may produce a laxative effect or mucosal irritation.

8.3 Preparation of Standard Calibration Curve of Metoclopramide HCl

8.3.1 Preparation of Buffer Solution

Simulated gastric fluid (SGF) without enzyme was prepared according to the USP [107]. 2.0 g of sodium chloride was dissolved in 7.0 mL of hydrochloric acid and sufficient DI water added to make 1000 mL. 1.2 of pH adjusted using digital pH meter (Fig. 8-1).

Figure 8-1: SevenMulti Mettler-Toledo® AG (SN: 1230065338) digital pH meter

8.3.2 Preparation of Standard Stock Solution

Standard stock solution was prepared by accurately weighed 10 mg of MTH using digital balance and transferred to a 500 ml volumetric flask. 250 mL of simulated gastric fluid was added to the same volumetric flask and swirled for solublization. The drug was dissolved completely and the final volume was adjusted with SGF up to 500 mL. This solution has a concentration 20 µg/mL and was used as standard stock solution. From this standard stock solution, serial dilutions were made by using SGF in order to have a concentration of 2, 4, 6, 8, 10, 15, and 20 µg/mL, and the absorbance of the diluted solutions were measured to construct the calibration curve.

8.3.3 Preparation of Sample Solutions

5 mL sample solutions were prepared to have a concentration of 2, 4, 6, 8, 10, 15, and 20 µg/mL. The standard stock solution was used as the highest concentration of the

linearity range study.   The required concentrations of sample solutions were prepared

from the standard stock solution based on the following equation 8.1:

Amount of drug (µg) = Conc. of drug (µg/ml) X Vol. (ml)   (Equation 8.1)

X = 15 µg/ml * 5 ml (needed) = 75 µg → vol. need from stock = 75/ 20 = 3.75 ml

from the stock solution → final vol. required – vol. withdraw from stock →

5 – 3.75 = 1.25 ml of SGF needed to make a standard solution of **15 µg/ml in 5 mL**

X = 10 µg/ml * 5 ml (needed) = 50 µg → vol. need from stock = 50/ 20 = 2.5 ml from

the stock solution → final vol. required – vol. withdraw from stock →

5 – 2.5 = 2.5 ml of SGF needed to make a standard solution of **10 µg/ml in 5 mL**

X = 8 µg/ml * 5 ml (needed) = 30 µg → vol. need from stock = 40/ 20 = 2 ml from

the stock solution → final vol. required – vol. withdraw from stock →

5 – 2 = 3 ml of SGF needed to make a standard solution of **8 µg/ml in 5 mL**

X = 6 µg/ml * 5 ml (needed) = 30 µg → vol. need from stock = 30/ 20 = 1.5 ml from

the stock solution → final vol. required – vol. withdraw from stock →

5 – 1.5 = 3.5 ml of SGF needed to make a standard solution of **6 µg/ml in 5 mL**

X = 4 µg/ml * 5 ml (needed) = 20 µg → vol. need from stock = 20/ 20 = 1 ml from

the stock solution → final vol. required – vol. withdraw from stock →

5 – 1 = 4 ml of SGF needed to make a standard solution of **4 µg/ml in 5 mL**

X = 2 µg/ml * 5 ml (needed) = 10 µg → vol. need from stock = 10/ 20 = 0.5 ml from

the stock solution → final vol. required – vol. withdraw from stock →

5 – 0.5 = 4.5 ml of SGF needed to make a standard solution of **2 µg/ml in 5 mL**

8.3.4 Measurement of Absorbance and Calibration Curve

Metoclopramide hydrochloride is a UV absorbing molecule that has specific chromophore which absorb at a particular wavelength. It was successfully quantified by using Agilent G1103A UV-Vis Spectrophotometer (Fig. 8-2). The absorbance of solutions containing 10μg/ml was determined in UV range 200-800 nm using SGF as blank. The λ_{max} was found to be at 272 nm (Fig. 8-3). At this wavelength maximum, calibration curve was drawn by plotting graph between absorbance and concentration.

Figure 8-2:   Agilent G1103A UV-Vis Spectrophotometer, figure.3 (SN: CN22808134), Agilent Technologies, Shanghai.
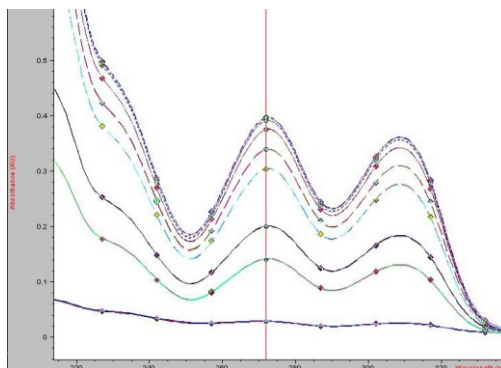

Figure 8-3:   Spectrum of metoclopramide hydrochloride (2-20 μg/mL)

Calibration curve data were constructed in the range concentrations 2 to 20 μg/mL. Beer's law was obeyed over this concentration range. According to the law, the absorbance is directly proportional to the path length (b) and the concentration (c) of the absorbing material [109]. Equation 8.2 describes the calculation of absorbance:

$$A = \varepsilon b c \qquad \text{(Equation 8.2)}$$

Where (A) is the absorbance; (ε) is the molar absorption coefficient; (b) is the path length; and (c) is the concentration. For a quantitative determination of analyte species of unknown concentrations in a solution, a calibration curve of absorbance versus concentration of known analyte concentrations must be constructed with linear regression. The absorbance for the MTH can be measured using UV-Vis and the concentration can be extrapolated from the calibration curve [110].

8.4 Preparation of MTH Powder Mixtures with Superdisintegrants

Preparation of MTH orally disintegrating tablets was occurred by using two superdisintegrants excipients Primojel® and Polyplasdone XL®. Tablet 8.8 describes the class, mechanism of action, and some consideration that should be taken when using them.

Tablet 8.8: List of superdisintegrants that used in ODT preparation [26]

Superdisintegrants	Class	Mechanism Of action	Comment
• Sodium starch glycolate • Explotab® • Primogel®	Cross linked starch (sodium starch glycolate)	➢Water uptake followed by rapid swelling ➢Swells 7-12 folds in less than 30 sec.	➢Effective conc. 4-6% ➢ Swells in three dimensions and high level serve as sustain release matrix
• Crosspovidone • Crosspovidon M® • Kollidon® • Polyplasdone®	Cross linked polyvinyl pyrrolidone (Crospovidone)	➢Both swelling and wicking	➢Water insoluble and spongy in nature so get porous tablet.

Preparation of orally disintegrating tablets containing 100 mg of powder mixtures were mixed according to tablet 8.9 for the superdisintegrants Primojel® and Polyplasdone XL®.

Table 8.9:   Orally disintegrating mini-tablets of formulation included the API and active pharmaceutical ingredients

Ingredients	Quantity per tablet (mg)					
	F1	F2	F3	F4	F5	F6
Metoclopramide HCl	10	10	10	10	10	10
Microcrystalline cellulose	40	40	40	40	40	40
Trehalose	43	41	39	43	41	39
Polyplasdone XL® (crospovidone)	3	5	7	---	---	---
Primojel® (sodium starch glycolate)	---	---	---	3	5	7
Talc	3	3	3	3	3	3
Magnesium Stearate	1	1	1	1	1	1
Total weight	**100**	**100**	**100**	**100**	**100**	**100**

For each powder mixture of superdisintegrants, trehalose as the bulk/diluent excipient was ground in a mortar with a pestle (Fig. 8-4) to create a free-flowing powder and break up any agglomerated particles. Then, it was mixed with microcrystalline cellulose as binder, talc and glidant and lubricant by using V-Shell blender (Fig. 8-5) for 20 minutes to ensure through mixing and phase homogenization. Finally, the blend was lubricated using magnesium stearate as a lubricant and continued mixing for another 5 minutes.
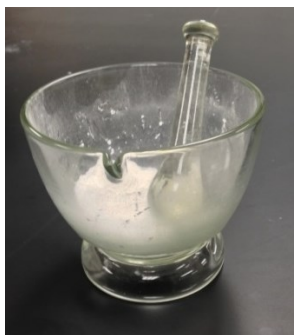
Figure 8-4: Mortar with a pestle provided by the University of Toledo
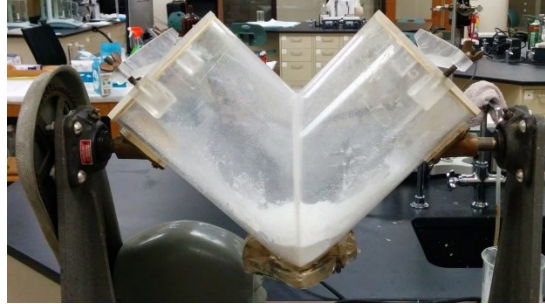
Figure 8-5: V-Shell blender provided by the University of Toledo

8.5 Physical Evaluation of Prepared Blend for Compression

8.5.1 Angle of Repose

The angle of repose was determined according to a recommended procedure described in USP 36. The peak of the cone may be misshaped by the strength of the powder flowing from the funnel. Therefore, the height of the funnel should be maintained approximately 2-4 cm from the top of the powder pile as it is being formed in order to minimize the impact of the falling powder on the tip of the cone [72]. The angle of repose was then calculated according to the USP by measuring the height and the base of the heap of powder formed and using equation 6.1 as following:

$$\tan(\alpha) = \frac{\text{height}}{0.5 \times \text{base}}$$ (Equation 6.1)

Equation 6.2 helps to determine and angle of repose by rearranging Equation 6.1:

$$(\alpha) = \tan^{-1} \times \frac{\text{height}}{0.5 \times \text{base}}$$ (Equation 6.2)

8.5.2 Loose Bulk Density (LBD)

This is the ratio of the total mass of powder to the bulk volume of powder [26]. Accurately weigh a portion of powder mixture (40 g) and transfer it to a 100 ml

graduated cylinder. The mixture was carefully leveled without compacting, and read as the unsettled apparent volume (V_o) [24]. Loose bulk density can be calculated based on equation 6.3 and expressed in g/ml:

$$\textbf{Loose Bulk Density } (\boldsymbol{\rho_{bulk}}) = \frac{\textbf{mass of powder}}{\textbf{unsettled volume } V_o} \qquad \textbf{(}\text{Equation 6.3)}$$

8.5.3 Tapped Bulk Density (TBD)

This is the ratio of total mass of the powder to the tapped volume of the powder [26]. Accurately weigh some quantity of powder mixture (40 g) and transfer it to a 100 ml graduated cylinder. The cylinder containing the sample was manually tapped. The final tapped volume (V_f) was then measured to the nearest graduated units. Tapped bulk density can be calculated based on equation 6.4 and expressed in g/ml:

$$\textbf{Tapped Bulk Density } (\boldsymbol{\rho_{tapped}}) = \frac{\textbf{mass of powder}}{\textbf{final tapped volume } V_f} \qquad \text{(Equation 6.4)}$$

8.5.4 Compressibility Index (Carr's Index)

Equation 6.5 describes the calculation of the Compressibility Index of the powder mixture by using bulk density and tapped density. It measures the powder flowability and is expressed in percentage [24]:

$$\textbf{Compressibility Index } (\%) = \textbf{100} \times \left[\frac{(\rho_{tapped} - \rho_{bulk})}{\rho_{tapped}} \right] \qquad \text{(Equation 6.5)}$$

8.5.5 Hausner Ratio

The Hausner ratio is a number that is correlated to the flowability of a powder or granular material. [24]. It is an indirect index to measure the ease of powder flow [26]. Equation 6.6 describes the calculation of Hausner Ratio.

$$\textbf{Hausner Ratio} = \frac{\rho_{tapped}}{\rho_{bulk}} \qquad \text{(Equation 6.6)}$$

Figure 8-6 illustrates A Flowratex, Lab EXC model PF-21-101-150, that used determine the angles of repose and 100 mL graduated cylinder that used to determine loose and tapped bulk density.

Figure 8-6:   A Flowratex, Lab EXC model PF-21-101-150 and 100 mL graduated
               cylinder provided by the University of Toledo

8.6 Formulation of Orally Disintegrating Tablets of MTH

After the preparation of metoclopramide hydrochloride powder mixture as described in section 6.4, orally disintegrating tablets of MTH were prepared according to the formula given in table 6.3 by direct compression method. A 100 mg of MTH ODTs were manufactured by compressing the powder blend with 5.64 mm round, convex

tableting punch set using a Manesty A28 Tableting Press, (Fig. 8-7). The compression force was adjusted to produce tablets with a hardness of 35-45 N.

Figure 8-7: Manesty Tablet Press Machine LTD., (Liverpool, England) No. 2L187

8.7 Evaluation of Orally Disintegrating Tablets of MTH

8.7.1 Tablet Appearance

Twenty tablets of each formulation were tested to check any discoloration or surface roughness in tablet formulation.

8.7.2 Weight Variation

Ten (10) tablets of each batch formulation were selected randomly and weighed in grams individually and accurately using digital balance. Figure 8-8 illustrates an Intelligent Weighing Technology's model PM-300 balance, Intelligent Weighing Technology, Inc. (Camarillo, CA).

Figure 8-8: Intelligent Weighing Technology's model PM-300 balance

8.7.3 Tablet Hardness and Thickness

It is the force required to break the tablet into halves by compression in the diametrical direction. Ten (10) tablets were selected randomly and measured individually for thickness and hardness using Sotax Hardness Tester [81]. The tablets measured in mm for the thickness and Newton (N) for the breaking force using USP Standard method. Figure 8-9 illustrates Sotax Hardness Tester [81] Model HT1 4127.013, Sotax Corp. (Switzerland) in Newtons (N) that was provided by the University of Toledo.

Figure 8-9: Sotax Hardness Tester

8.7.4 Tablet Friability

The tablet friability test determination was achieved accodring to the United States Pharmacopeia and National Formulary (USP 36-NF 31) using an Erweka Friability Apparatus (Fig 8-10). The test measured to simulate shipping and packaging stress. The USP 36 recommends the total tablet sample should be taken corresponding as near as possible to 6.5 g for tablets with a unit weight equal to or less than 650 mg. The tablets were carefully dedusted prior to testing. Accurately the tablet samples were weighed (recorded as initial weight), and placed in the drum. The drum was rotated up to 100 revolutions at 25 rpm for 4 minutes [24, 78, 79]. After that time lapse, any loose dust was removed from the table samples by using a brush, and accurately reweighed (recorded as final weight). Equation 6.8 describes the calculation of friability percentage [7]:

$$\textbf{Friability } (\%) = \frac{(\textbf{weight}_{\textbf{initial}} - \textbf{weight}_{\textbf{final}})}{\textbf{weight}_{\textbf{inital}}} \times \textbf{100} \qquad \text{(Equation 6.8)}$$

If obviously cracked, cleaved, or broken tablets were present in the tablet sample after tumbling, the sample fails the test. If the results are difficult to interpret or if the weight loss is greater than the targeted value, the test should be repeated twice and the mean of the three tests determined. The maximum mean weight loss from the three samples is not more than 1.0% which is considered acceptable for most products [80]

Figure 8-10:   Erweka Friability Apparatus Model TAP 23644,
               Erweka (Western Germany)

8.7.5 In-vitro Disintegration Time Test

The test was carried out on six tablet using DI water at 37±5 °C   as a medium and Erweka disintegration apparatus (Fig. 8-11) according to USP 36-NF 31standard basket method with disks [78]. Each tablet should be placed in each of the six tubes of the disintegration basket   apparatus, one disc was added to each tube, and run for disintegration time [85]. The time was measured in seconds for complete disintegration of the tablet with no palpable mass remaining in the apparatus. At the end of the time limit specified in the monograph, lift the basket from the fluid, and observe the tablets. According to the test, all of the tablets must disintegrate completely within one minute. In case if one or two tablets fail to disintegrate completely, the test must be repeated at least on 12 additional tablets. The USP requires at least 16 of the total of 18 tablets that tested are disintegrated [86].

Figure 8-11:   Erweka Disintegration Apparatus Model: ZT2 No: 27151(Western
                Germany)

8.7.6 Simulated Wetting Time Test

Table 5.4 illustrates the optimum volume of the blue dye solution for a given tablet size that has been established by Park, J.H., et al. Based on the previous experimental studies to develop a modified disintegration time test for ODTs, the wetting time test in this research has compared two modified methods. Small dry sponges (1cm x 1cm in size) and Whatman filter paper disk (21mm in diameter) were placed in each in the well of corning 12-well polystyrene microplates (22 mm in diameter). The wetting time test was performed by adding Brilliant Blue 85 E 133 solution to the distilled water to make a blue dye solution, which will enable suitable visual end-point detection for water uptake. 1.25 mL of blue dye solution was placed in well to make the sponges and Whatman filter paper wet. Then, the ODTs were transferred carefully and placed on the wet surface them in each well using a pair of forceps. Finally, the wetting time was measured when the blue color reach completely to the center of the upper surface of ODTs. Wetting time test was performed on triplicate of each batch and all results were reported as mean ± SD. A lower wetting time implies a quicker disintegration of the tablet. Figure 8-12 and 8-13 illustrate the wetting time test equipment before and after the absorption of blue dye solution.

Figure 8-12: Wetting time test equipment before ODTs absorption of blue dye solution

Figure 8-13: Wetting time test after ODTs absorption of blue dye solution

8.7.7 In-vitro Dissolution Test

In-vitro dissolution test of metoclopramide hydrochloride ODT was performed triplicate for each batch using simulated gastric fluid (SGF) and AT 7smart Dissolution Apparatus from SOTAX (Fig. 8-14). It is a dissolution apparatus that compliant with all pharmacopeia methods including USP 1,2,5,6, [111]. 900 mL of the hydrochloric acid buffer of pH 1.2 was used as dissolution medium. The paddle speed was adjusted to rotate at 50 rpm. The temperature of dissolution medium was maintained at 37±0.5ºC throughout the experiment. One MTH orally disintegrating tablet was placed in each flask of dissolution apparatus. Aliquot of 5 mL was withdrawn at predetermined time interval (10, 20, 30, 40, 50 seconds, 1, 2, 4 and 6 min.). The collected samples were analyzed at λ_{max} 272 nm using the dissolution medium (SGF) as blank in order to determine metoclopramide hydrochloride concentration. The cumulative percentage amount of drug release was calculated and plotted against time.
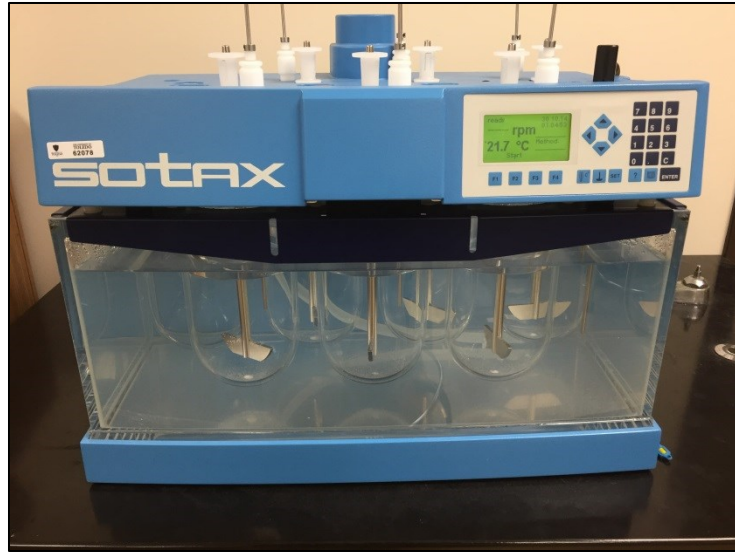
Figure 8-14: AT 7smart Dissolution Apparatus SOTAX dissolution apparatuses.

8.8 Tablet Packaging

White plastic jars with black lid screw top and amber cello were used for the ODT Packaging. Tablets were packaged using a JVM Automatic Tablet Distributing & Packing System Model ARP-350SL6, JVM Co, Ltd. (Korea). Each package contained four 10 mg metoclopramide HCl tablets. The packaging was composed of 2.5 inch amber cello and thermal paper to create a heat seal (University of Toledo Medical Center, OH). For the white plastic jars, tablets were packaged by putting the tablet inside the jar and use Aluminum Foil beneath the black lid for sealing. Figure 8-15 illustrates the two packaging systems, amber cello (A) and white plastic jars (B) for the ODTs formulation in the final product.
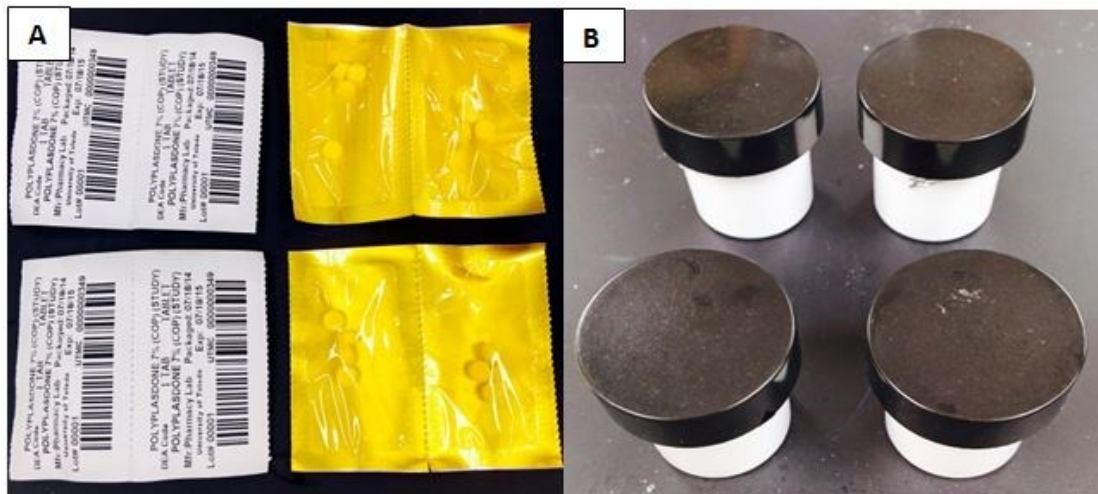
Figure 8-15: Tablet packaging systems. (A) Amber cello and (B) White plastic jars

8.9 Accelerated Stability Study of Optimized Batch

Accelerated stability studies for orally disintegrating tablets were established according the ICH guidelines. The change in in-vitro release profile on storage was determined for the optimized batch. It was subjected to the stability studies for eight weeks on both packaging systems and stored under the following conditions:

- $25 \pm 2°C$ and the relative humidity (RH) should be $60\% \pm 5$.

- $40 \pm 2°C/$ and the relative humidity (RH) should be $75\% \pm 5$.

Relative humidity chambers were established by creating an excess of water soluble salt in contact with its saturated solution in baby food jars (Fig. 8-16) according to the CRC Handbook of Chemistry and Physics [112-115], and the temperature of $40\pm2°C$ was achieved by keeping the baby food jars in the oven. The tablets were withdrawn after weeks 1, 2, 3, 4, 5, 6, 7, and 8 to analyze the physical-chemical properties such as appearance (any color change or visual defect), hardness, and dissolution release test.

The collected data was compared with the initial obtained data of the tablets analysis [43, 45, 89, 90, 116].

Figure 8-16: Relative Humidity Chamber for MTH orally disintegrating tablets

Chapter 9

Results and Discussion

Metoclopramide HCl (MTH) orally disintegrating mini-tablets were prepared using various ratios of superdisintegrants by direct compression. The superdisintegrants Primojel® and Polyplasdone XL® were used in various concentrations, namely 3%, 5%, and 7% to formulate the orally disintegrating mini-tablets of MTH.

The absorbance of the diluted solutions for MTH was measured using UV-Vis and the concentrations were extrapolated from the calibration curve [110]. Table 9.1 represents the linearity range study of MTH in simulated gastric fluid at 272 nm.

Table 9.1: Linearity range study of MTH in SGF without enzyme at 272 nm.

Sample No.	Aliquot of MTH. concentration (µg/mL)	Absorbance (nm)			Average ± SD
		Reading I	Reading II	Reading III	
1	20	0.7529	0.7536	0.7562	0.7544±0.0016
2	15	0.5563	0.5557	0.5624	0.5578±0.0025
3	10	0.3629	0.3650	0.3657	0.3647±0.0010
4	8	0.2921	0.29131	0.3051	0.2958±0.0062
5	6	0.2132	0.21442	0.2153	0.2143±0.0010
6	4	0.1343	0.13812	0.1383	0.1368±0.0020
7	2	0.0661	0.0674	0.0673	0.0669±0.0006

Figure 9-1 illustrates the constructed calibration curve for MTH. The linearity was found to be between 2-20 µg/mL. Equation 9.1 describes the regression equation

that was obtained from the sample solutions. The correlation coefficient (R^2) of the standard curve was found to be 0.9998 which established high linearity.

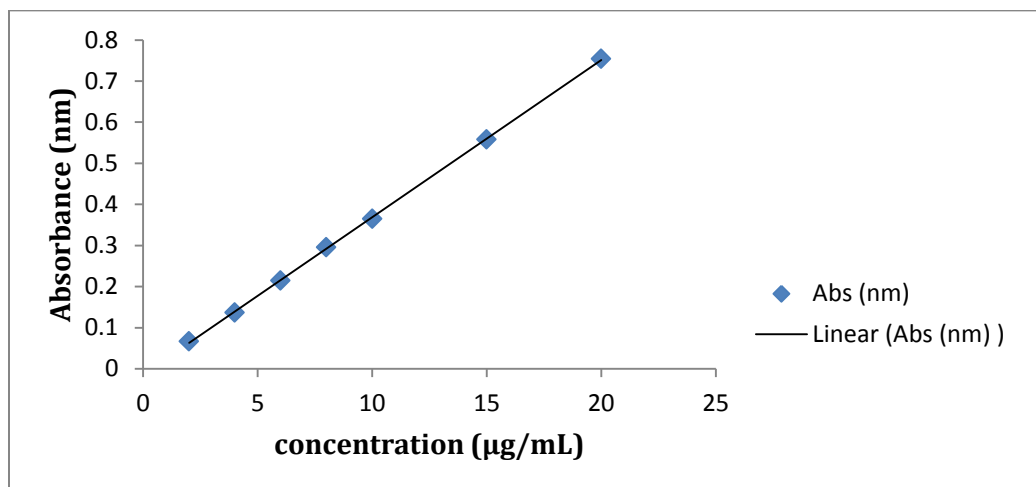$$Y = 0.0383X - 0.0137 \qquad \text{(Equation 9.1)}$$

Figure 9-1:   Absorbance values in nm for standard calibration curve of Metoclopramide HCl in simulated gastric fluid without enzyme at λ_{max} of 272 nm where slope = 0.0383; intercept = -0.0137; and R^2 = 0.9998

For direct compression, the flowability of the powder blend is very important. Therefore, two methods were used for powder flowability measurements. The bulk density and tapped density for the powder blends were determined to calculate the Hausner ratio and Carr's index. The second method for flowability characterization was to determine the angle of repose.

Table 9.2 provides the data obtained for the angle of repose for all the batches prepared. The values were found to be in the range of 31.96 to 34.82, which indicates good flow property for the powder blend according to the USP [72].

Table 9.2:   Flow properties of the powder blends: angle of repose value and
             flowability, mean ± standard deviation (n=3).

Formulation	Flow properties	
	Angle of repose	According to USP
F1	31.96±0.38	Good
F2	32.49±0.80	Good
F3	32.58±0.46	Good
F4	34.82±1.86	Good
F5	33.79±1.82	Good
F6	34.31±1.14	Good

Table 9.3 provides the data obtained for the Carr's index and Hausner ratio for all

the formulation batches. The bulk density and tapped density for all the batches varied

from 0.51to 0.55 g/mL and 0.62 to 0.74 g/mL, respectively. Carr's index values were

found to be in the range of 22.86 to 25.77, which is satisfactory for the powders as well

as implies that the blends have good compressibility. Hausner ratio values obtained were

in the range of 1.30 to 1.35, which shows a passable flow property for the powder blend

based on the USP [72].

Table 9.3:   Flow properties of the powder blends: bulk and tapped density, Carr's
             index, and Hausner ratio, mean ± standard deviation (n=3).

Formulation	Density (g/ml)		Flow properties		
	Bulk	Tapped	Carr's index	According to USP	Hausner ratio
F1	0.51±0.002	0.67±0.001	24.30±0.16	Passable	1.32±0.003
F2	0.48±0.001	0.62±0.002	22.86±0.216	Passable	1.30± 0.004
F3	0.50±0.001	0.67±0.002	25.25±0.346	Passable	1.34±0.006
F4	0.54±0.001	0.73±0.005	25.64±0.506	Passable	1.34±0.009
F5	0.55±0.001	0.74±0.001	25.67±0.890	Passable	1.34±0.016
F6	0.55±0.001	0.74±0.002	25.77±0.304	Passable	1.35±0.006

Table 9.4 displays the evaluation parameters for metoclopramide hydrochloride

orally disintegrating mini-tablets such as appearance, weight variation, thickness, height,

hardness, friability, disintegration time, and drug content.

ODTs were prepared and examined visually for shape and color. A white color and concaved surface with circular shape was observed after compressing the formulations. All tablets passed the weight variation test and were found to be within the acceptable limit according to the USP (±10%) [76]. The results for tablet thickness and height for all batches was found to range from 5.72 to 5.75 mm and 3.66 to 3.98 mm, respectively. Hardness or breaking force of tablets for all batches was found to range from 34.8 to 43.6 N. Tablet formulations must show good mechanical strength with sufficient hardness in order to handle shipping and transportation. Friability values for all the formulations were found to be in the range of 0.24 % to 0.40 %. The results obtained were found to be within the acceptable range (<1%), indicating sufficient mechanical integrity and strength for the prepared tablets according to the USP [80]. The disintegration time test was used based on the USP [86]. According to the test, all of the tablet formulations should disintegrate completely within one minute which indicates faster disintegration. The percent drug content for all the formulations were calculated by measuring the absorbance at the wavelength 272 nm, and was found to be between 98.50% to 102.18%, which is within the acceptable limits as per USP [75].

Table 9.4: Evaluation parameters of MTH orally disintegrating mini-tablets.

Formulation	Weight variation[α](mg)	Thickness[α] (mm)	Height[α] (mm)	Hardness[α] test (N)	Friability test (%)	Disintegration time [*] (sec)	% Drug content [β]
F1	101.9±4.09	5.75±0.05	3.98±0.02	34.8±4.57	0.40	19.0±1.00	100.95±6.03
F2	104.7±1.16	5.73±0.03	3.91±0.02	40.5±6.02	0.24	15.7±1.53	102.18±1.97
F3	101.5±2.46	5.74±0.04	3.89±0.02	39.8±2.90	0.29	12.7±1.53	101.59±1.75
F4	104.4±1.17	5.72±0.04	3.77±0.03	43.6±2.95	0.40	38.3±4.73	98.87±0.56
F5	103.3±1.42	5.73±0.03	3.80±0.03	35.8±2.78	0.27	24.7±2.52	101.01±2.45
F6	100.9±1.79	5.75±0.02	3.66±0.03	38.6±9.03	0.24	50.7±2.52	98.50±0.85

α: each value represents the mean ± standard deviation (n=10).
β: each value represents the mean ± standard deviation (n=3).
*: Disintegration time must be less than 1 minute according to the USP monograph

Table 9.5 provides the in-vitro drug release profile for all the formulation (F1 to

F6). The ODT formulation for MTH showed an average range of 98.50 to 102.2 % drug

release at the end of 6 minutes. Figure 9-2 illustrates the comparative in-vitro drug

release profile for metoclopramide HCl for formulations F1 to F6. It was observed that

only the formulations with Polyplasdone XL (F1, F2, and F3) took the shortest time to

release more than 92% of the drug at the end of 1 minute.

Table 9.5:   Comparative in-vitro drug release (cumulative percent release) values of
              formulation codes F1 to F6. Each value represents the mean ± standard
              deviation (n=3).

Time (min)	Cumulative Percent Drug Release of All Formulations					
	Polyplasdone XL 3% (F1)	Polyplasdone XL 5% (F2)	Polyplasdone XL 7% (F3)	Primojel 3% (F4)	Primojel 5% (F5)	Primojel 7% (F6)
0	**0**	**0**	**0**	**0**	**0**	**0**
0.08	4.43±1.96	4.61±0.84	5.87±1.48	5.86±1.34	6.38±0.37	6.48±0.06
0.16	6.43±2.47	10.85±1.29	6.87±1.07	5.98±1.23	7.51±1.47	6.69±1.45
0.25	13.01±2.19	22.65±8.42	16.12±3.74	6.85±2.25	11.60±4.54	7.95±0.04
0.33	30.27±0.73	42.25±13.5	26.23±6.27	9.10±3.35	14.63±8.23	9.57±1.25
0.41	48.79±8.55	53.20±10.2	45.49±11.1	12.24±5.03	20.43±8.31	10.59±1.08
0.5	71.88±5.49	69.14±6.78	63.09±17.6	18.23±9.55	28.89±11.6	14.08±1.56
0.66	83.95±3.20	82.15±4.74	76.51±7.03	27.55±14.9	51.26±22.7	19.84±2.61
0.83	90.82±2.45	89.27±0.72	89.34±1.79	39.09±21.8	62.25±27.4	26.70±4.42
1	**94.40±1.32**	**92.97±1.42**	**95.34±1.17**	**51.89±24.2**	**74.26±30.4**	**29.67±2.89**
2	99.74±4.89	100.45±1.51	100.35±1.59	86.13±7.01	97.30±2.53	50.40±9.80
4	100.19±5.50	101.53±1.48	101.37±1.65	97.37±0.43	100.01±1.29	87.44±14.1
6	100.9±6.03	102.2±1.97	101.6±1.75	98.87±0.56	101.0±2.45	98.50±0.85
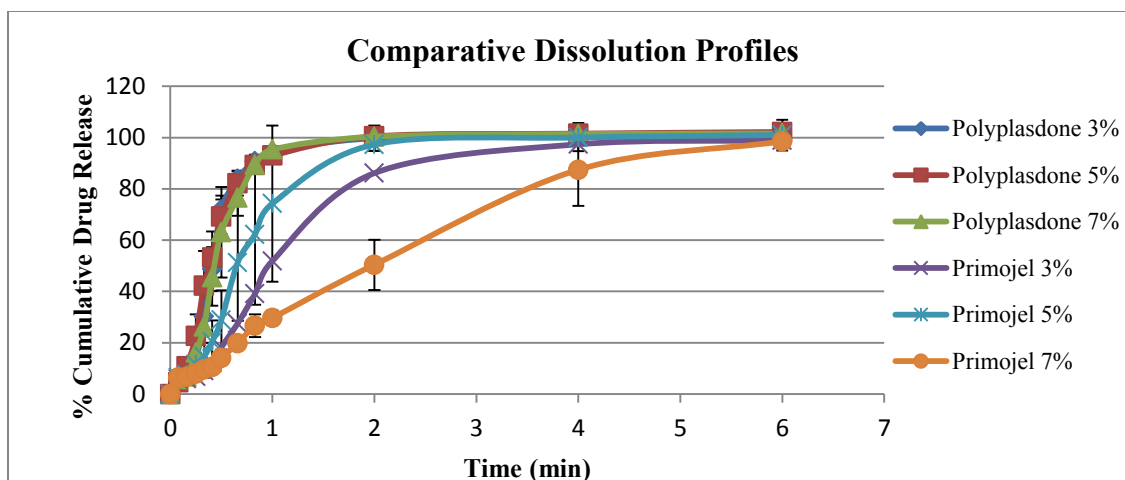
Figure 9.2:   Comparative in-vitro drug release profile of Metoclopramide HCl for formulations F1 to F6

Table 9.6 illustrates the wetting time test to determine the time taken for the water to wet the whole tablet. It was performed by comparing two methods modified for the disintegration time test. The first method uses a sponge, the wetting time range for all batches was found to be in the range of 0.57 to 11.2 minutes. It was observed that only the formulations with Polyplasdone XL (F1, F2, and F3) had a faster time to wet the tablet when comparing it with the other formulations (F4, F5, and F6) which used Primojel as the superdisintergrant. The second method used Whatman filter paper, the wetting time range for all batches was found to be in the range of 2.67 to 20.67 seconds.

Table 9.6:   Evaluation Comparison of modified disintegration time tests between sponge and Whatman filter paper, each value represents the mean ± standard deviation (n=3).

Formulation	Wetting Time	
	Sponge (min)	Whatman filter paper (sec)
F1	0.57±0.049	2.67±0.58
F2	2.13±0.690	5.67±4.62
F3	0.73±0.384	5.33±2.31
F4	11.2 ±1.23	10.6±4.73
F5	8.38±1.60	7.00±4.40
F6	5.09±1.40	20.67±4.16

Currently, there is no a specific disintegration test for ODTs based on the USP and EP. The results from the USP disintegration test <701> do not provide a strong correlation with in vivo disintegration times in the mouth. The test uses a disintegration medium of about 900 mL of water and a vigorously oscillating apparatus which cannot provide the condition that is found in vivo [86]. Furthermore, there is no USP method for evaluating the disintegration time for ODTs that represents in vivo disintegration time in the mouth based on the test method reported in the 2th Annual FDA Science Forum [82]. Therefore, FDA recommends using a modified form of the USP disintegration test <701>.

There are several modified disintegration test methods which have been developed for ODTs. However, most of them do not provide a good in vitro - in vivo correlation (IVIVC) because the experimental conditions used do not simulate the wet tongue surface condition or the amount of saliva in the mouth at a given time. These are key points in assessing the disintegration time of ODTs in the mouth. The rate of saliva is 0.2-0.4 mL/min when resting and can increase to as much as 2 ml/min when stimulated. Therefore, the average rate of saliva secretion is about 0.5-0.7 mL/min [82, 117]. Using a wet sponge to simulate the wet tongue tissue can provide a better IVIVC in order to determine the wetting time test comparing it with Whatman filter paper.

When performing the comparative drug release studies, dissolution profiles were analyzed using pair-wise procedures (model-independent methods) namely, the difference factor (f1) and similarity factor (f2). ANOVA two-factor with replication test and two-factor without replication test were used in order to determine if there is a significant different using two different superdisintegrants with various ratios. The

difference factor (f1) is the percentage difference between two curves at each point and is a measurement of the relative error between the two curves. The similarity factor (f2) is a measurement of the similarity in the percent (%) dissolution between the two curves. If (f1) is between 0 and 15 and (f2) is between 50 and 100, the dissolution profiles are considered similar and bioequivalent[118]. Table 9.7 shows the values determined for the difference factor and similarity factor when comparing the two different superdisintegrant dissolution profiles between the groups.

Table 9.7: Comparison of the dissolution profiles between the groups

Formulations	Difference factor (f1)%	Similarity factor (f2)%
Polyplasdone XL 3% vs. Primojel 3%	38.74	25.36
Polyplasdone XL 5% vs. Primojel 5%	25.83	34.04
Polyplasdone XL 7% vs. Primojel 7%	49.64	21.39

Table 9.8 gives the values for the difference factor and similarity factor when comparing Polyplasdone XL superdisintegrant dissolution profiles at different ratios within the groups.

Table 9.8:   Comparison of the dissolution profiles of Polyplasdone XL superdisintegrants within the groups at different ratios

Formulations	Difference factor (f1)%	Similarity factor (f2)%
Polyplasdone XL 3% vs. Polyplasdone XL 5%	5.37	65.65
Polyplasdone XL 3% vs. Polyplasdone XL 7%	4.59	70.88
Polyplasdone XL 5% vs. Polyplasdone XL 7%	6.93	61.20

Table 9.9 shows the values for the difference factor and similarity factor when comparing Polyplasdone XL superdisintegrant dissolution profiles at different ratios within the groups.

Table 9.9:   Comparison of the dissolution profiles of Primojel superdisintegrants
within the groups at different ratios

Formulations	Difference factor (f1)%	Similarity factor (f2)%
Primojel 3% vs. Primojel 5%	20.22	45.40
Primojel 3% vs. Primojel 7%	26.38	44.70
Primojel 5% vs. Primojel 7%	56.48	31.76

According to the data obtained above for the difference and similarity factor for the dissolution profiles for the formulations, it was observed that the dissolution profile between the two superdisintegrants were significantly different. ANOVA: two-factor with a replication test provided a p-value of 0.014 (p<0.05) which indicated that a significant difference in the dissolution release profiles, as depicted in Figure 9.2 when comparing Polyplasdone XL and Primojel as the superdisintegrant used in the ODT formulation. Polyplasdone XL superdisintegrants demonstrate a much faster release compared to the Primojel.

According to the values provided in Table 9.8, the values for F1 and F2 for Polyplasdone XL superdisintegrant were between 0-15 and 50-100, respectively. Comparisons of the dissolution profiles for Polyplasdone XL superdisintegrant within the groups when used in different ratios were shown to have similar release profiles. Moreover, ANOVA: two-factor without replication test indicated there was no significant different (p>0.05) in the dissolution release profiles using different ratios of Polyplasdone XL superdisintegrant.

The values in Table 9.9 gave the difference factor F1 located above 15% and similarity factor F2 below 50% which indicated there was a significant difference in the dissolution release profiles using different ratios of Primojel superdisintegrant. In addition, ANOVA: two-factor without replication test indicated there was a significant

difference (p<0.05) in the dissolution release profiles using different ratios of Primojel superdisintegrant.

Primojel 3% and Primojel 5% formulations were shown to have similar release profiles as well. Primojel 3% and Primojel 7% exhibited a similarity of release. However, Primojel 5% and Primojel 7% showed a significant difference in their dissolution profiles.

Based on data analysis for the tablet evaluation, the various impact on the flow properties for blend, friability, disintegration time, wetting time, and drug release behavior of the tablets lead to selecting an optimized formulation for the batch. Eventually, Formulation 3 (Polyplasdone XL 7%) was selected for accelerated stability studies.

Table 9.10 provides the evaluation parameters for the optimized batch that used amber cello blister package upon storage condition at 25°C/ RH 60% for eight weeks. The evaluation of the short-term stability studies included physical appearance, weight variation, thickness, hardness, disintegration time, and drug content. Figure 9.3 shows the changes in drug content over time for the cello blister package.

Table 9.10:   Stability studies evaluation parameters for the optimized batch.

Time (weeks)	Physical appearance	Weight variation$^{\alpha}$ (mg)	Thickness$^{\alpha}$ (mm)	Hardness$^{\alpha}$ test (N)	Disintegration time * (sec)	Drug content $^{\beta}$
Week 1	No changes	100±2.04	5.71±0.01	28.2±2.40	33.3±2.52	100.6±3.71
Week 2	No changes	100±1.65	5.71±0.01	26.3±3.08	33.7±5.03	95.08±4.70
Week 3	No changes	99.0±2.00	5.70±0.01	27.5±2.66	33.0±7.55	98.60±2.67
Week 4	No changes	102±1.52	5.71±0.01	26.2±3.31	28.7±2.52	101.2±4.35
Week 5	No changes	101±2.73	5.72±0.01	24.2±3.92	29.7±3.06	93.57±1.69
Week 6	No changes	100±1.81	5.68±0.02	22.7±1.03	28.7±2.52	96.19±5.66
Week 7	No changes	97.7±1.77	5.68±0.01	26.0±3.03	26.7±2.52	101.2±3.03
Week 8	No changes	98.0±1.49	5.69±0.007	26.8±3.76	21.7±2.52	99.75±1.19

α: each value represents the mean ± standard deviation (n=10).
β: each value represents the mean ± standard deviation (n=3).
*: Disintegration time must be less than 1 minute according to the USP monograph
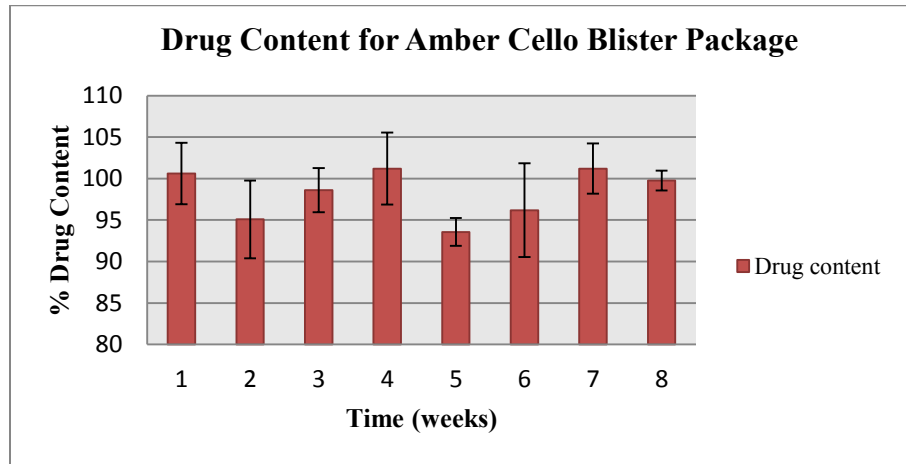
Figure 9.3:   Statistical analysis of drug content at 25°C/ 60% RH for Amber Cello
                Blister Package, the mean ± SD (98.27±2.96).

Figure 9-4 illustrates the comparative in-vitro dissolution profiles for the optimized batch that used amber cello blister package upon storage conditions at 25°C/ RH 60% over eight weeks.

Figure 9-4:   Comparative in-vitro drug release profile for the optimized batch at 25°C/ 60% RH for Amber Cello Blister Package.

Table 9.11 provides the evaluation parameters for the optimized batch that used plastic jars as packaging upon storage conditions at 25°C/ RH 60% for eight weeks. The evaluation of the short-term stability studies included the physical appearance, weight variation, thickness, hardness, disintegration time, and drug content. Figure 9-5 displays the changing of drug content over the time for the plastic jars packaging.

Table 9.11:   Stability studies evaluation parameter for the optimized batch

Time (weeks)	Physical appearance	Weight variation[α] (mg)	Thickness[α] (mm)	Hardness[α] test (N)	Disintegration time * (sec)	Drug content [β]
Week 1	No changes	103±2.74	5.68±0.01	37.2±6.05	32.6±3.51	103.1±5.67
Week 2	No changes	103±1.23	5.69±0.01	36.2±3.66	32.7±7.51	102.3±3.18
Week 3	No changes	104±2.04	5.68±0.01	39.7±5.28	33.7±6.51	97.69±3.95
Week 4	No changes	104±2.16	5.69±0.01	41.0±6.69	36.7±3.51	99.16±1.11
Week 5	No changes	103±2.71	5.70±0.01	34.3±7.06	32.3±4.16	99.53±2.33
Week 6	No changes	100±2.02	5.76±0.01	22.7±1.37	30.7±3.21	94.08±0.82
Week 7	No changes	102±2.22	5.67±0.01	37.3±4.93	31.0±2.00	95.33±0.96
Week 8	No changes	102±2.72	5.68±0.01	38.0±3.41	29.0±2.00	95.52±3.80

α: each value represents the mean ± standard deviation (n=10).
β: each value represents the mean ± standard deviation (n=3).
*: Disintegration time must be less than 1 minute according to the USP monograph.
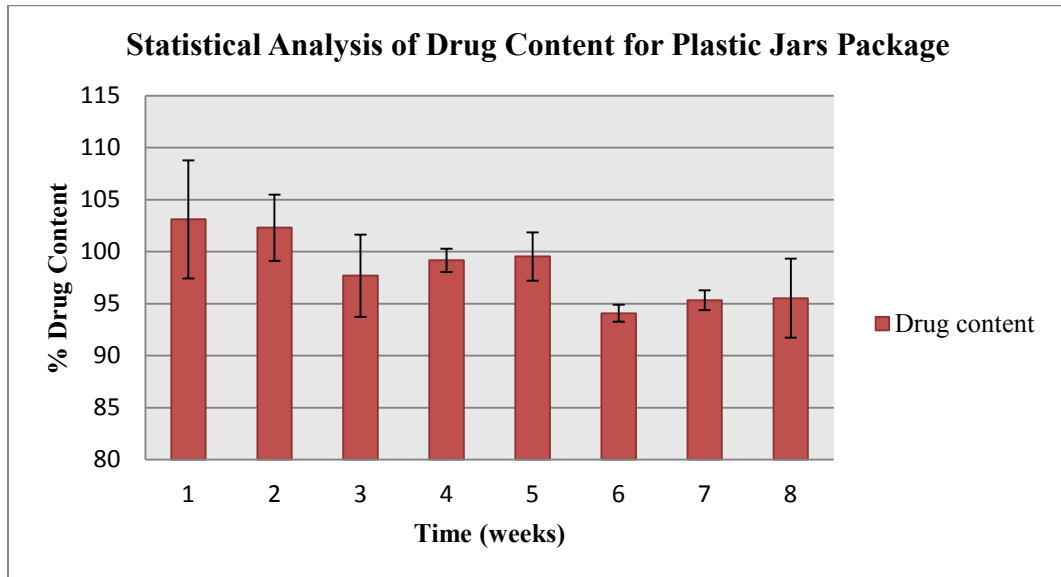
Figure 9-5:   Statistical analysis of drug content at 25°C/ 60% RH for Plastic Jars
               Package, the mean ± SD (98.33±3.30)

Figure 9-6 illustrates the comparative in-vitro dissolution profiles for the optimized batch that using amber cello blister packaging upon storage conditions at 25°C/ RH 60% over eight weeks.
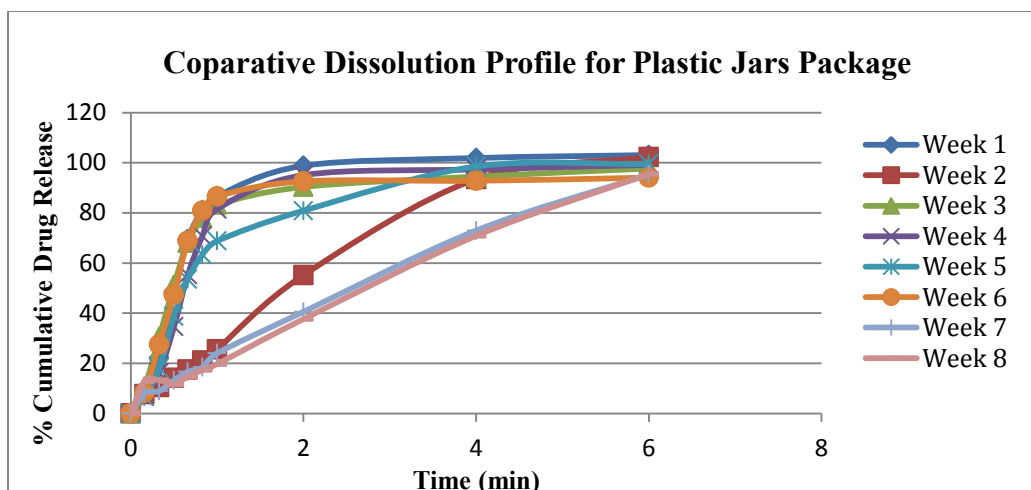
Figure 9.6: Comparative in-vitro drug release profile for the optimized batch at 25°C/ 60% RH for the plastic jars Package

Table 9.12 provides the evaluation parameters for the optimized batch using plastic jar packaging upon storage conditions at 40ºC/ 75% RH for eight weeks. The evaluation of the short-term stability studies included the physical appearance, weight variation, thickness, hardness, disintegration time, and drug content. Figure 9-7 shows the changing drug content over the time frame for plastic jar packaging.

Table 9.12: Stability studies evaluation parameter for the optimized batch.

Time (weeks)	Physical appearance	Weight variation$^{\alpha}$ (mg)	Thickness$^{\alpha}$ (mm)	Hardness$^{\alpha}$ test (N)	Disintegration time * (sec)	Drug content $^{\beta}$
Week 1	No changes	102±2.33	5.75±0.01	25.3±5.65	40.3±3.21	91.95±3.69
Week 2	No changes	102±2.56	5.73±0.01	24.0±3.16	28.3±3.51	98.77±1.22
Week 3	No changes	101±3.24	5.75±0.01	17.2±2.93	29.7±7.02	101.0±1.13
Week 4	No changes	103±1.64	5.76±0.01	19.5±2.81	30.7±5.51	99.38±0.24
Week 5	No changes	104±1.23	5.78±0.01	14.0±2.28	39.3±3.21	97.45±2.90
Week 6	No changes	100±1.57	5.67±0.01	38.2±2.71	27.3±2.08	101.1±3.50
Week 7	No changes	100±1.84	5.78±0.04	16.2±1.60	32.7±4.51	99.67±4.12
Week 8	No changes	102±3.37	5.78±0.01	15.8±2.14	30.3±2.08	93.90±3.88

α: each value represents the mean ± standard deviation (n=10).
β: each value represents the mean ± standard deviation (n=3).
*: Disintegration time must be less than 1 minute according to the USP monograph.

Drug Content at 40°C/ 75% RH for Plastic Jars Package
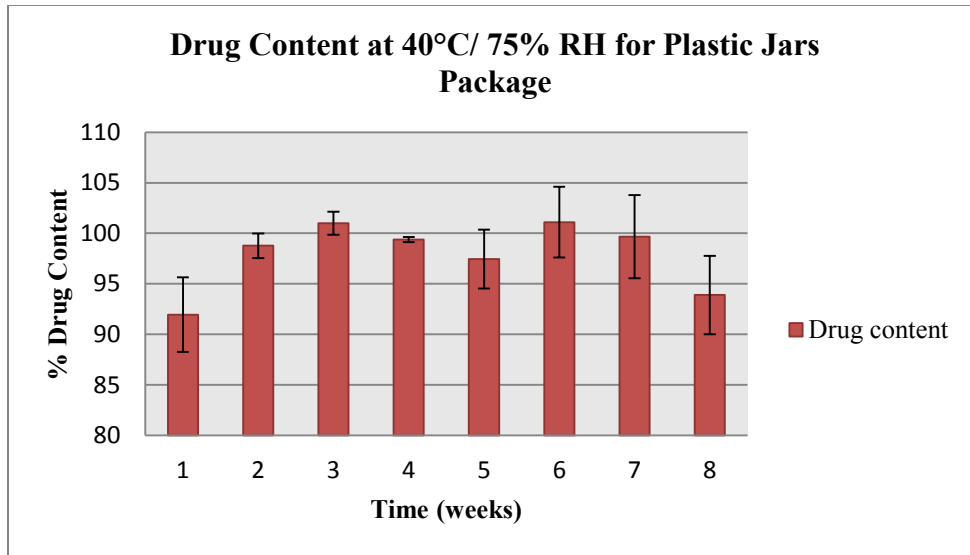
Figure 9-7:   Statistical analysis of drug content at 25°C/ 60% RH for Plastic Jars Package, the mean ± SD (97.90± 3.33)

Figure 9-8 illustrates the comparative in-vitro dissolution profiles for the optimized batch that using amber cello blister packaging upon storage conditions at 40°C/ RH 75% over eight weeks.
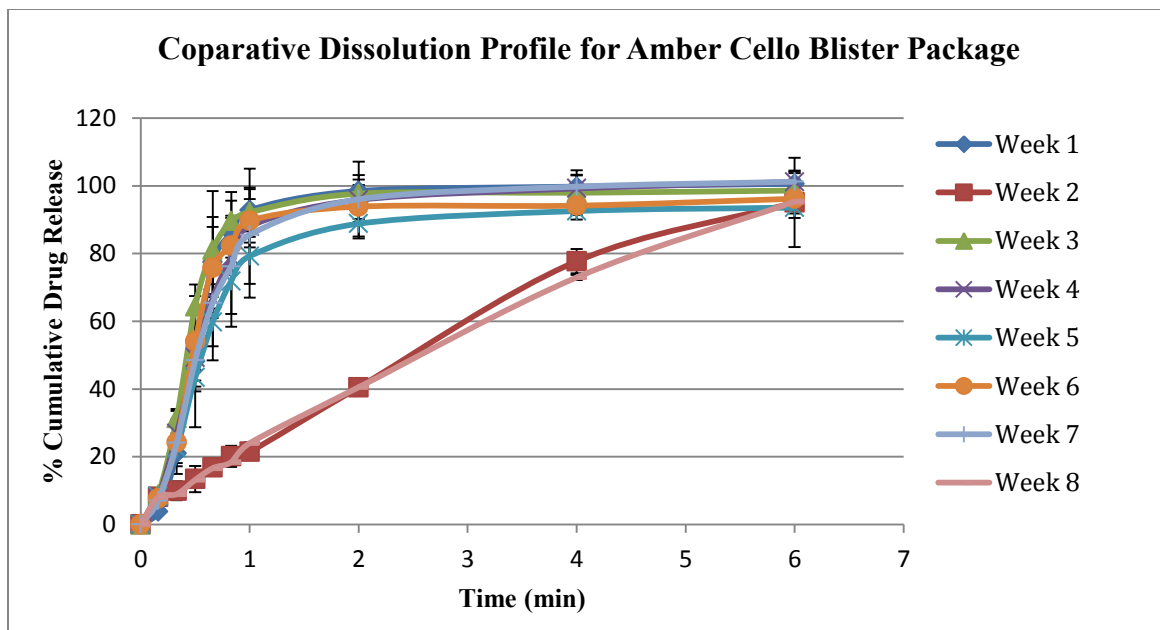

Coparative Dissolution Profile of of Stability Studies for Optimized Batch at 40°C/ 75% RH for Plastic Jars Package
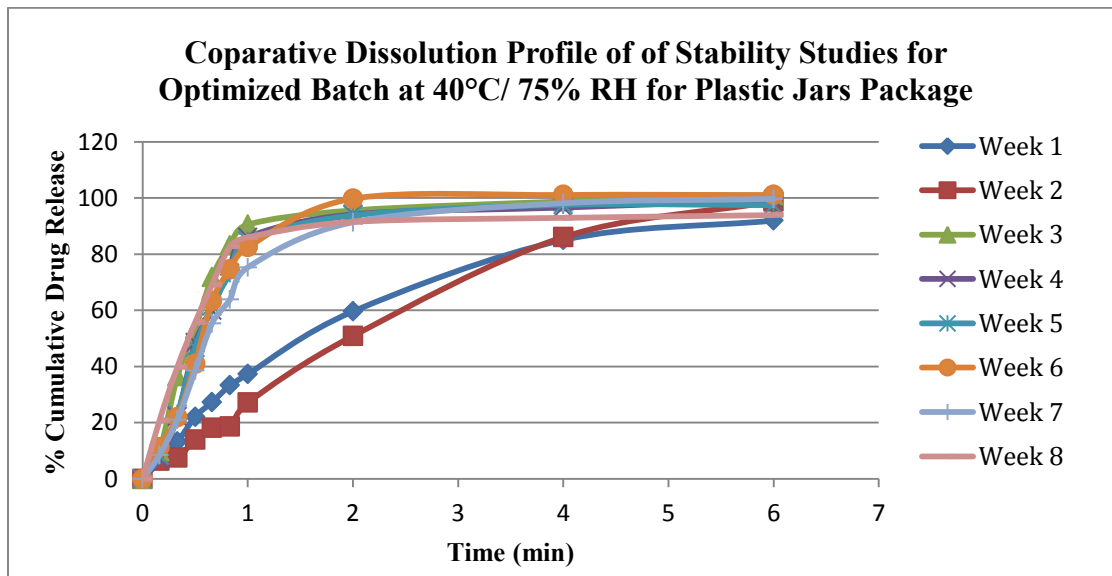
Figure 9-8:   Comparative in-vitro drug release profile for the optimized batch at 40°C/ 75% RH for Plastic Jars Package.

Figure 9-9 illustrates the failure of the stability studies for the optimized batch which used amber cello blister packaging upon storage conditions at 40°C/ RH 75% from week one to week eight.

Figure 9-9:   Failure of the formulation to pass the stability studies which used amber cello blister packaging upon storage conditions at 40°C/ RH 75%

The data revealed for the stability studies concerning the packaging systems indicate that the amber cello blister and plastic white jar packaging stored at room temperature (25°C) with relative humidity (60% RH) can provide stability for the optimized formulation.   There were no changes in the physical appearance during storage.   Tablet dimension with regard to thickness and height were stable.   The formulation passed the weight variation and disintegration test.   Drug content was determined to be acceptable within the allowed limit.

For the amber cello blister and plastic white jar packaging stored in the oven at 40°C/ RH 75%, the cello blister failed to protect the formulation which allowed the tablets to turn into a powder. This is reasonable since the cellophane substance is permeable to the humidity which explains the failure of amber cello blister packaging in the oven at high humidity (75% RH). However, the plastic jar packaging showed a better preservation and protection for the ODT formulation for MTH. Drug content was found to be acceptable within the allowed limit.

Chapter 10

Conclusion and Future Work

10.1 Conclusion

The orally disintegrating mini-tablets of Metoclopramide HCl (MTH) were successfully formulated.   Various ratios of superdisintegrants were used to prepare the formulation by direct compression. The superdisintegrants Primojel$^{®}$ and Polyplasdone XL$^{®}$ were used in various concentrations, namely 3%, 5%, and 7% in order to achieve the optimized batch.

The orally disintegrating mini-tablets of MTH were prepared using the above superdisintegrant excipients and evaluated for pre-compression parameters such as bulk density, tapped density, Carr's index, Hausner's ratio and angle of repose. Post-compression parameters such as weight variation, hardness, friability, disintegration time, wetting time, dissolution analysis, drug content uniformity, and finally accelerated stability studies for the optimized batch were also evaluated.

In the beginning, the powder blends for the formulations were evaluated using their flowability property. Carr's index values were found to be satisfactory for the powders as well which suggest that the blends had good compressibility. Hausner ratio

values obtained were shown to be a passable flow property for the powder blend based on the USP.

Orally disintegrating tablets were compressed in order to have sufficient mechanical strength and integrity to withstand handling, shipping and transportation. The formulation was shown to have a rapid disintegration time that complied with the USP (less than one minute). The mixing of powders and compression yielded an acceptable limit for the percent drug content. An optimized batch was achieved and it was determined to contain Polyplasdone XL 7% because it showed a faster drug release in the dissolution profile and a rapid disintegration time. Accelerated stability studies were accomplished in order to optimize the batch using two different packaging systems with two temperatures and relative humidity conditions for eight weeks. The data obtained from the stability studies indicated that the orally disintegrating mini-tablets of MTH were stable under different environmental storage conditions.

10.2 Future Work

The orally disintegrating tablet dosage form is a promising future for drug delivery with the advancement in pharmaceutical excipients such as superdisintegrants. More superdisintegrants can be further investigated with different excipients after the determination of drug-excipients compatibility study. The optimized batch can be subjected for long period of time on stress conditions in order to determine the shelf life of the product. The result of this batch can be conducted also to the human trials to investigate the taste of the formulation and the dissolution drug release in the in-vivo environment. Comparison of similarity studies can be done on the formulation by using the brand drug available in the market.

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