An-Najah National University

Faculty of Graduate Studies

INFLUENCE OF FOOD INDUCED VISCOSITY ON DISSOLUTION AND DISINTEGRATION OF TABLETS: EFFECT OF FORMULATION AND PROCESS PARAMETERS ON TABLET MANUFACTURED BY WET GRANULATION

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Dedication

In the Name of Allah, the most Merciful, the most Beneficent. Praise be to the almighty Allah of all worlds. Prayers and peace be upon our Prophet, Muhammad, his family and all of his companions. I announce the last step of my thesis,

I'd want to dedicate this beautiful labor and effort to two lovely people who have provided me with a wealth of information and skill, but they won't be able to rejoice with me because they have passed away.

Raja Zalmout, my aunt and my Idol, was my motivation and educational hero.

My father-in-law, Zahi Ameireh, from whom I gained wisdom, I pray that Allah Almighty gathers us all in Paradise.

I also dedicate this work to my parents, who have dedicated all of their time to seeing me become a very successful man; truly, all I am today is due to the amazing prayers they have always offered for me.

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Finally, and most importantly, I cannot begin to convey my unending thanks and love to my wonderful family, who were with me every step of the way, supporting me in every way.

Declaration

I, the undersigned, declare that I submitted the thesis entitled:

INFLUENCE OF FOOD INDUCED VISCOSITY ON DISSOLUTION AND DISINTEGRATION OF TABLETS: EFFECT OF FORMULATION AND PROCESS PARAMETERS ON TABLET MANUFACTURED BY WET GRANULATION

I declare that the work provided in this thesis, unless otherwise referenced, is the researcher's own work, and has not been submitted elsewhere for any other degree or qualification.

Student's Name: Zain Al-Abedin Zanoon

Signature:

Date: 5/6/2023

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INFLUENCE OF FOOD INDUCED VISCOSITY ON DISSOLUTION AND DISINTEGRATION OF TABLETS: EFFECT OF FORMULATION AND PROCESS PARAMETERS ON TABLET MANUFACTURED BY WET GRANULATION

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Abstract

Postprandial elevation in gastric viscosity may retard tablet disintegration and delay drug dissolution from solid dosage forms, resulting in a significant decrease in drug bioavailability thereby affecting the therapeutic efficacy. This may be critical especially for medication where rapid onset of action is required. Deep understanding of the critical processing parameters on tablet disintegration and drug dissolution under fed conditions will help in designing a formulation with minimum viscosity mediated negative food effects.

The current research aims to study the impact of formulation and processing factors on tablet disintegration and release of Active Pharmaceutical ingredient (API) under both fasting state and fed states. The effect of different types of fillers was investigated in different formulations: Lactose monohydrate, corn starch and Microcrystalline cellulose (MCC), as well as, Di-calcium phosphate dehydrate. Wet granulation is a critical manufacturing step for oral solid dosage forms. Wet granulation method was applied in the preparation of ten immediate release formulations with Paracetamol serving as the model drug. The effects of wet granulation parameters such as: the mode of incorporation of disintegrant and the type of the granulating solvent were highlighted.

The study concluded that filler type is found to affect tablet disintegration: MCC based formulations gave the quickest drug disintegration in simulated fasted state, but they were the worst under viscous media. Lactose and Dicalcium Phosphate (DCP) based formulations provide rapid disintegration under fed state. Formulations prepared by using alcohol as solvent of granulation had shorter disintegration times compared to

formulations using water in both fasting and fed states. The addition of Sodium Starch Glyclolate (SSG) intra-granularly results in shorter disintegration time compared to the extra-granular counterparts under fed condition.

The study recommends that: the obtained results highlight the importance of formulation excipients (filler type) and manufacturing parameters on tablet disintegration. This study will provide guidance that help in design and development of formulation with minimal food effect.

Keywords: Behaviour; Disintegration; Dissolution; Even Formula; Fasting State; Fed State; Odd Formula.

Chapter One

Introduction

1.1 Background

Food effects on the rate and extent of drug absorption from oral pharmaceutical solid products often constitute an important aspect affecting therapeutic outcomes. Postprandial elevation in gastric viscosity have a direct retarding impact on tablet disintegration thus slowing the release rate from solid dosage forms, resulting in a significant decrease in drug bioavailability. (1–3) It is for this reason that large sums are often invested into conducting food effect studies on human subjects during bioavailability and/or bioequivalence (BE) evaluation.

Therefore, increasing the degree to which formulation performance is independent of food effects will not only reduce the incidence of compliance-related therapeutic outcomes, but could also make product development less costly in both economic and ethical terms.

Evidence of food induced viscosity on drug dissolution and tablet disintegration is well documented. (1–4) It has been shown previously, that different formulations have shown strongly varying degrees of sensitivity to food induced viscosity increase in vitro.

In the work of Radwan et al, three commercially available immediate release (IR) tablet formulations of Trospium chloride (highly soluble drug) showed such varying degrees of sensitivity to viscosity increase that the rank order of the formulations dissolution rates was changed between fasted and fed state dissolution conditions. (4)

Viscosity effect on dissolution of various Trospium chloride tablet products on checking out the release on the point 15 minutes on fasting state and on the point 120 minutes on Fed state as follows:

on the time interval 15 minutes Spasmolyt have shown 98% release on Fasting state Spasmex have shown 75% releasee and 89% were noticed as the release from the product Trospi. In fed state however the percentage of release of all products Spasmolyt, Spasmex and Trospi were 38%, 55% and 58 % respectively.

It is noteworthy that Spasmolyt® and Trospi® satisfy the very rapid dissolving criterion for IR products under fasted state conditions whereas under viscous conditions Trospi® shows approx. a 1.5-fold higher release rate than Spasmolyt® after two hours (58% vs. 38%). And Spasmex® which fails to satisfy the very rapidly dissolving criterion exhibits roughly 1.45-fold higher release compared to Spasmolyt® under viscous conditions (55% versus 38%).

This indicates that formulation factors can have strong influence on the degree to which food can affect the release properties of an IR formulation. This makes BE in the fasted state no solid guarantee of BE under fed conditions. (1–4)

In the work of Zaheer and Langguth, they made some explorations in this regard by studying the effect of fillers and disintegrants as well as compression force on tablet disintegration and dissolution. They observed that high microcrystalline (MCC) content resulted in substantial retardation of disintegration and dissolution when the tablets are tested under fed or fasted state simulating conditions. This was explained by the impairment of the capillary wicking based uptake of liquid by the insoluble MCC. With regard to the disintegrants, it was found that sodium starch glycolate exhibits particularly poor disintegration inducing abilities under viscous conditions, which is probably a result of it gelling tendency worsening a water uptake that has already been slowed down by medium viscosity. (5–8)

Deeper understanding of this phenomenon would help to outline the critical formulation and processing parameters affecting the degree to which food –induced viscosity rise affects product performance. This will in turn enable formulators to develop products of highly soluble compounds (for poorly soluble compounds there is the issue of food effect on compound solubility, which introduces a new dimension) the bioavailability from which is food-independent. So the focuses of this research will be mainly on excipients that have an impact effect on disintegration and dissolution of tablets. This needs a

thorough understanding of the multitude of mechanisms through which food components interact with oral drug products.

1.2 Oral Drug Absorption

Tablets account for more than 80% of all drugs consumed by humans globally. (9) Solid tablet formulations administered orally travel through the GI system before releasing into systemic circulation. Once in the stomach and upon contact with GI fluid, tablets begin to disintegrate, breaking down into tiny pieces, after which the granules are dissolved in the GI secretions (Figure 1). Following the dissolution step; the drug permeates through the membrane of the small intestine, traveling through the portal vein to the liver, where it undergoes hepatic metabolism. After which, the active pharmaceutical ingredient (API) or it metabolites enter the systemic circulation to produce the desired therapeutic effect.

Food may alter the oral bioavailability of a drug by inducing physiological changes such as: gastric emptying rate, gut motility, the composition and the viscosity of the GI fluid, pH of the GIT, bile stimulation, and luminal metabolism alterations. (10)

Food may have significant impact on the rate of drug release by affecting the physicochemical characteristics of API. Food may alter the solubility of the API. Moreover, a substantial interaction between the API and food components may occur, resulting in a decline in the AUC curve as a result of reduced bioavailability. (11–20)

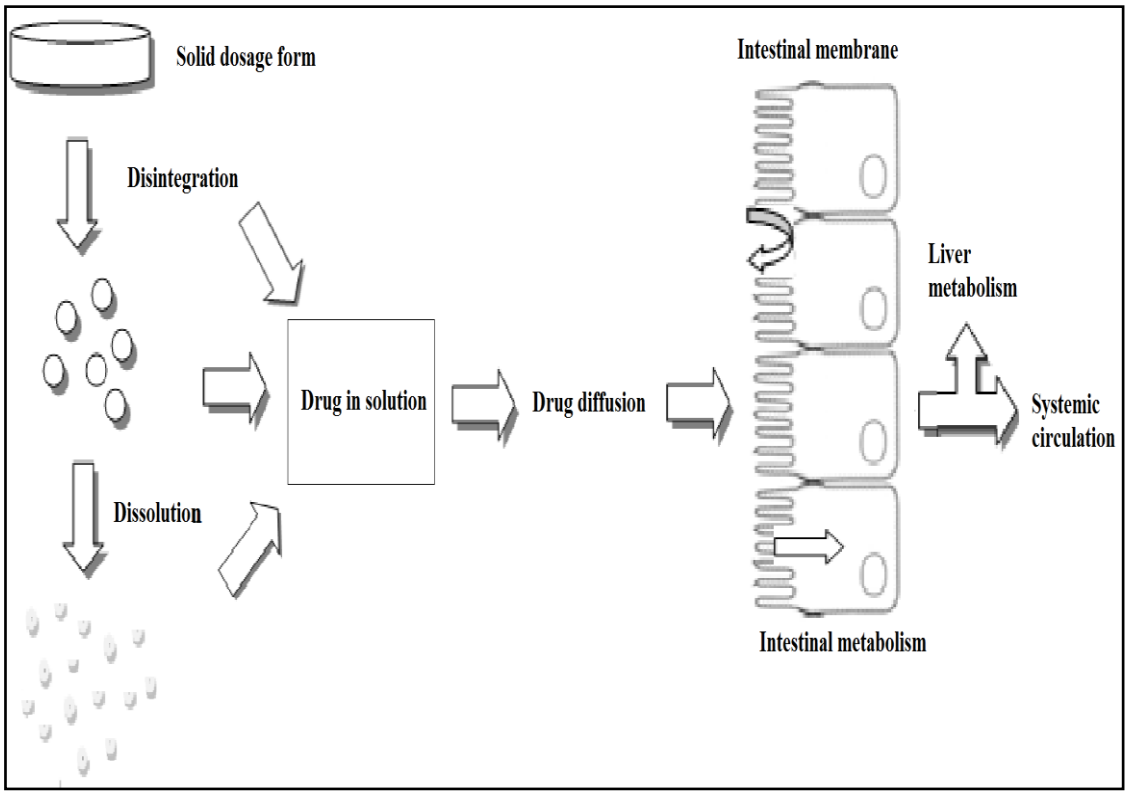
Tablet disintegration and drug dissolution are critical steps of the drug absorption process. Any delay in these steps will affect the overall drug absorption kinetics.

Concomitant intake of food was found to retard tablet disintegration and dissolution rate of BCS class 3 drugs. Several studies have demonstrated the impact of postprandial viscosity on the drug release and tablet disintegration. An inverse relationship was shown between increased luminal viscosity and tablet dissolution, which was explained in part by impaired water ingress into tablets under viscous conditions.

Food effect is influenced by many factors such as; the physicochemical properties of the drugs, the formulation type of excipients, composition of meal and its caloric content. (21)

Figure 1

Scheme for oral drug absorption steps: disintegration, dissolution, permeation and metabolism



1.3 Tablet Disintegration

Immediate release tablets are designed to undergo rapid disintegration into small particles when exposed to GI fluids, which results in an increase in surface area available for dissolution and subsequently absorption. Disintegration is considered the first step in the drug release and absorption process. That's why disintegration is considered critical for drug in vivo performance.

For tablet to disintegrate, a breakdown of the bond connecting the granules together is required. There is a liquid flow towards the tablet's passage, but this flow is driven by other mechanisms that provide a force greater than the force linking the granules.

As a result, the process or significance of disntegrant in the tablet can never be neglecte d since it impacts bioavailability. This is critical for determining whether the appropriate dosage of the drug has already been released, absorbed, and then the systemic bloodstream is given the intended percentage of Bioavailability

1.3.1 Mechanisms of Tablet Disintegration

Several mechanisms have been proposed to explain the disintegrant action: wicking, swelling, heat of wetting, particle repulsion and deformation recovery.

Among these mechanisms, swelling and wicking (capillary action) are the most reported in the literature followed by disruption of particle bonds, and strain recovery.

The intermolecular bonds connecting the granules together is connected through different type of force, however breaking down the bonds connecting the granules together is achieved by the flow of liquid towards the tablet's passage, but this flow is driven by other mechanisms that provide a force greater than the force linking the granules together. (22,23)

Wicking through capillary action and swelling by bursting and interrupting the inter and intra molecular bonds have been identified as the major 2 mechanisms of Disintegration. By controlling the quantity and knowing which way exactly the disintegrant should be incorporated to the formula, both mechanisms might work produce synergism effect which potentiate the force needed to break the bonds connecting the granules ending by decreasing the time required to complete disintegration. (24,25)

1.3.1.1 Wicking

Wicking is the process where water or disintegration medium ingress into the internal and micro structure of the tablet by capillary action and thus air is displaced by the flow of medium. (26) The mechanism of wicking does not only include the flow of water by capillary action through the pores, but it also includes the hydrophilic network that formed by the action of disintegrant agent, which provide extra channels for water to ingress through, thus more water flow is achieved by the action of wicking, ended by weakening the internal structure of the tablet. (27)

H-Bond, Van der Waals and electrostatic forces are all broken due to the permeation of water under the process of wicking, although this will weaken the internal structure of the tablet, but wicking is not the only cause of disintegration.

Many researchers believe that the penetration of water by the mechanism of wicking is the most important step to initiate disintegration. (28)

1.3.1.2 Swelling

Swelling is the increase of volume of the compressed particles, this expansion will impart extra stress on the adjacent particles, and many mechanisms were reported in literature to explain the exact mechanism of Swelling. (29)

The breakup of the tablet occurs exactly on a point when the pressure of expanding particles became higher than the pores of the tablet, such increase in the volume create extra pressure that cause the breakup of the tablet causes the tablet to disintegrate. (28,30,31)

1.4 Factor affecting tablets disintegration

Tablet Disintegration may be affected by a variety of factors, such as: formulation composition and excipient, manufacturing process parameters and media viscosity.

1.4.1 Media viscosity effect on drug dissolution and tablet disintegration

Postprandial elevation of gastric viscosity has a direct negative impact on tablet disintegration slowing the release rate from solid dosage forms, resulting in a significant decrease in drug bioavailability.

Evidence of food induced viscosity on drug dissolution and tablet disintegration is well documented. Prolonged tablet disintegration in human gastric juice was reported by Abott et al., who presumed that this delay is mainly due to the rise in the viscosity of human gastric fluid. (32)

Anwar and the coworker have attributed delayed tablet disintegration in milk due to its viscosity. (33) Khoury and colleagues have ascribed the delay in dissolution rates of hydrocortisone alcohol in dilute polymeric media to the decreased diffusivity in viscous media. (34) Film formation around the surface of tablet was proposed to explain the delayed tablet disintegration in the presence of food. This film acts as barrier preventing GI fluid from permeating into the tablet. (35) Food can cause an IR tablet to function like an enteric coated tablet. (36) Clarithromycin IR tablets showed longer disintegration

periods and lower dissolution rates in the presence of the homogenized standard FDA meal. (37)

Reduced wettability on the tablet surface, as well as hydrodynamic shear was identified as significant variables that delay the time required for complete disintegration in viscous media. (38)

The influence of viscosity-enhancing agents on oral absorption of metoprolol and bisoprolol was investigated. In vivo rat intestinal absorption experiments reveled reduced extent of drug absorption in (polyvinyl alcohol) PVA solution, due to reduced drug diffusion. (39)

Formulation factors may have strong influence on the degree to which food can affect the release properties of an IR formulation. In the work of Radwan et al, the disintegration study of three commercially available IR tablet formulations of Trospium chloride (highly soluble drug) showed such varying degrees of sensitivity to viscosity increase. The uncoated tablet (Trospi®) was least affected by an increase in the viscosity of the media. On the other hand, Film coated tablets (Spasmolyt®) showed comparatively longer disintegration times.

Formulation factors may contribute to the observed retardation behavior of tablet disintegration under fed condition, which in turn slows the rate of dissolution of IR tablets. The first step in tablet disintegration is water penetration into the tablet core brought about by capillary movement through the tablet's porous network, however high viscosity reduces the speed of capillary liquid movement, thus retarding compact disintegration. Moreover, in the case of a coated tablet, the interaction between a viscous medium and the hydrocolloid forming polymer in the coat results in the formation of a thick viscous barrier to the mass flow of the medium into the tablet. These observations pose the question of the critical formulation factors influencing this behavior.

1.4.2 Influence of formulation factors and Excipients on drug dissolution and tablet disintegration

Excipients may have an important role on the performance of the finished solid-dosage forms. Functional excipients added in solid oral formulations may improve or reduce the dissolution rate of the dr- ug. The typical excipients used in immediate-release formulas are disintegrants, fillers, binders, Surfactants and lubricants. Tablet disintegration may be affected by excipients properties such as mechanical characteristic, wettability, hydrophobicity, solubility and viscosity.

- **Cyclodextrin**

  Cyclodextrin is an example of excipients forming inclusion complexes with hydrophobic drug molecules and increasing their solubility. Cyclodextrins were shown to enhance the bioavailability of some anti-hypertension medications and diabetic drugs like glyburide. (40,41)

- **Surfactants**

  Surfactants are added in solid oral dosage forms to improve drug wettability and reduce the interfacial tension between the dissolution medium and the API. Sodium lauryl sulphate (SLS) was found to increase the solubility and dissolution rate of drugs such as celecoxib. (42)

- **Lubricants**

  Lubricants are hydrophobic excipients that have negative effect on tablet disintegration and drug dissolution rates. Mg-stearate is known to reduce the wettability of the formulations thus extending the time required for the tablet to fully disintegrate. (43)

- **Superdisintegrant**

  It is well known that superdisintegrant work strongly on breaking down the tablet entities which accelerate the process of dissolution, however, some of them have been found to reduce the rate of dissolution, potentially, this is assumed to the possible drug interaction with the superdisintegrant. (44,45)

Zaheer and Langguth have studied the effect of different types of superdisintegrant on the disintegration and dissolution of tablets containing highly soluble drug in fasted and fed simulated media. Three types of super disintegrant: Croscarmellose sodium, cross-linked polyvinylpolypyrrolidone, and sodium starch glycolate (SSG) were evaluated for their efficiency under viscous fed conditions. Tablets formulated using cross-linked polyvinylpolypyrrolidon provided the most rapid dissolution and disintegration rates in fed state. These findings were attributed to the non-gelling nature of disintegrant.

The disintegrant incorporated in least gelling characteristics was found to accelerate the disintegration time and vice versa.

- **Fillers or diluent**

  A diluent or filler is an inert excipient used to provide mass and volume of the solid oral dosage form. Filler make up to 70% of the total mass of the drug product by weight. Diluents are classified on the basis of their solubility into: water insoluble and water-soluble filler.

Lactose is water-soluble filler that is widely used in pharmaceutical solid oral formulations. There are several forms of Lactose available with differing physical properties: alpha-lactose monohydrate, beta-lactose (crystalline anhydrous lactose), amorphous lactose, spray dried lactose and agglomerated lactose.

Microcrystalline cellulose (MCC) is non-soluble filler with good swelling properties. MCC is one of the most frequently used fillers in pharmaceutical formulations due to its free-flow, compressibility and rapid disintegration properties.

Di Calcium Phosphate (DCP) is an-insoluble filler used in wet granulation and direct compression applications. DCP has good flowing properties as well as good compact ability. (46)

The solubility of the filler plays a major role in determining tablet disintegration. Disintegration times of tablets were found to vary with the variations in the solubility of the diluent. The use of soluble diluents (e.g. lactose and sucrose) in tablet formulations may contribute to rapid disintegration and dissolution of the drug. Aqueous soluble diluent work by attracting the dissolution medium into tablets and enhance the dissolution

of poorly soluble drug. In the work of Zaheer and Langguth, they made some explorations in this regard by studying the effect of fillers on tablet disintegration and dissolution. They observed that high content of microcrystalline cellulose (MCC) resulted in substantial retardation of disintegration and dissolution when the tablets are tested under Fed or Fasting simulating conditions. This was explained by the impairment of the capillary wicking-based uptake of liquid by the insoluble MCC. (5,6)

The high solubility of the filler does not always guarantee fast disintegration or dissolution properties. Disintegrant may perform better when formulated with insoluble fillers (e.g., dicalcium phosphate, MCC) than soluble fillers (e.g., lactose and mannitol). Quick disintegration was observed with tablets formulated by insoluble fillers. (47)

In previous study, drug dissolution from tablet formulated with soluble filler (lactose) was significantly lower compared to that formulation containing insoluble fillers (microcrystalline cellulose, MCC). This observation was attributed to the superior disintegration properties of MCC compared to the non-disintegrating lactose diluent, which are slowly dissolving from the surface of the tablets. The disintegration behavior of the MCC tablets may produce large contact area between drug particles and the medium. (48) Moreover, an increase in localized viscosity/ formation of a viscous barrier due to dissolved material of the soluble disintegrant agents is probably the reason behind impeded water penetration and delayed disintegration of tablet matrices.

1.4.3 Influence of manufacturing process on tablet disintegration and drug dissolution

The impact of processing parameters on the performance of the disintegrant has been highlighted in the literature. Wet granulation is the most widely used technique for granulation in pharmaceutical industry. It uses granulation binder solution to facilitate wetting and the agglomeration of powder bed. In a fluidized bed, high shear mixer or low shear mixer is used. The type of the granulation solvent is one of the most critical factors affecting granule properties. Water and alcohol are commonly used granulating solvent. The type of the solvent system may affect the wettability and solubility of formulation constituents, which in turn affects the granule properties and porosity. (49,50)

Moreover, the way of incorporation the disintegrant to the formula in wet granulation technique is of great importance. (51)

1.4.3.1 Effect of mode of incorporation of the disintegrant

Disintegrant is an essential component in tablet formulation that promotes rapid disintegration of solid dosage form upon contact with GI fluid. Disintegrant can be incorporated either intragranularly or extra granularly in wet granulated tablets.

The quantity of the disintegrant employed in the wet granulation formula and the method of super disintegrant incorporation in wet granulated tablets were found to have significant effect on the disintegration and dissolution rate of drugs. Some studies have reported that extra granular addition of disintegrant promotes faster disintegration compared to intragranularal addition. Gordon has found that drug dissolution from formulations prepared by extra granular incorporation of disintegrant was superior to those with intragranularly mode of inclusion. (52) In another study, the mode of incorporation of acid-modified water and white yam starch on the disintegration behavior of paracetamol tablet was evaluated. The result showed that tablets prepared with extra-granular addition of disintegrant had faster disintegration compared to intragranularly counterpart. (53)

Nazmi reported that the addition of sodium starch glycolate extra-granularly in wet granulation method had significantly enhanced the release profile of carbamazepine. (54) The previous findings were explained by the fact that when a superdisintegrant is integrated externally, the particles are positioned between the compressed granules; therefore, larger amount of the extra granular disintegrant is exposed to disintegration fluid, which results in rapid swelling and bursting of the disintegrant and the subsequent faster disintegration time.

On the other hand, other several studies showed that introducing the super disintegrant agent internally improve the dissolution of BCS Class 2 medicines by speeding disintegration, resulting in a ready API to be dissolved prior to absorption. (55–60) Yonni Eshovo Apeji evaluated the mode of incorporation of the superdisintegrant (sodium starch glycolate (SSG) and croscarmellose sodium (CCS)) on the tableting properties of

metronidazole. Tablets containing SSG or MCC incorporated intragranularly showed faster disintegration compared to extra granular incorporation. (61)

A superdisintegrant in the formula can further reduce the size of all particles after disintegration, thus rapid disintegration and dissolution is observed. (62)

1.4.3.2 Effect of the type of the granulation solvent

The effect of the type of the granulation solvents on the release characteristics of Paracetamol from hydroxypropylmethylcellulose (HPMC) matrix tablets was investigated. The dissolution rate of Paracetamol had the tendency to decrease as the water level in the granulation solvents increased. Addition of ethanol to water in the granulation solvent resulted in better dissolution properties when compared to water alone. (63)

The dissolution profile of MCC containing pellets was reported to be affected by the type of granulating solvent. In the work G.P Millili and J.B. Schwartz, the pellets prepared using ethanol demonstrated rapid disintegration with complete release in the dissolution medium, whereas, the water granulated pellets were found to remain intact for a long time. This was explained by water molecules binding with other excipients more strongly than ethanol. (64) Moreover, Ethanol granulated pellet have higher porosity with increased surface area which also plays another role in increasing the media uptake to the internal structure of the tablet and thus fasten disintegration.

Ethanol enhanced the dissolution of poorly soluble compounds threefold, particularly when the tablets were tested in Fasted State Simulated Intestinal Fluid (FaSSIF) in a pH 6.8 Buffer, This was done on a specific sort of poorly soluble medicine, where the concentration of these pharmaceuticals in the gut is enhanced due to their poor solubility. (64)

Another study that examined the influence of ethanol on wet granulation process discovered that the alcoholic solvent increased fluid permeability to the core of the tablet, According to the findings, granules created using a hydro-alcoholic binder solvent have higher porosity and permeability, The study's findings also indicated that the strength of granules made from water is greater than that of granules made from ethanol.

1.5 Aims and Objectives

This study was designed to improve our current knowledge of the role of formulation and processing parameters on drug release properties in the presence of food. The aspect of food induced viscosity was considered in this regard which was surprisingly not given the due importance.

The impact of the formulation and manufacturing process variables can be optimized to improve robustness of disintegration performance of tablets in fasted vs fed state conditions.

A screening phase was designed to figure out the important formulation and processing factors, which can be further optimized to minimize the negative food effect.

The specific goals were to evaluate:

- The effect of the nature of diluent type on in vitro tablet disintegration and drug dissolution under fast and fed conditions.
- The effect of the type of granulating solvent on drug release process using water and ethanol.
- The impact of mode of incorporation of the disintegrants on tablet disintegration using extragranular and intragranular modes.

The overall objective is to devise a formulation strategy for the development of formulations which will be least affected by the negative effect of food induced viscosity.

Chapter Two
Experimental

2.1 Introduction

This work is directed towards investigating the influence of the processing variables on the disintegration and drug release from the resulting tablets. Wet granulation is considered as an important processing step for oral solid dosage forms. In this study, wet granulation technique was employed in the preparation of ten formulations of an immediate release tablets. All the formulation contained Paracetamol as a model drug (325 mg / tablet), Polyvinylpyrolidone (K – 30) as binder (5%, w/w) and magnesium stearate as lubricant (1% w/w), Sodium starch glycolate as a disintegrant (3% w/w).

The effect of the nature of filler on tablet disintegration and drug dissolution under fast and fed conditions was investigated. Therefore, different types of filler were used: Lactose monohydrate, corn starch and MCC, as well as, Di-calcium phosphate dehydrate.

Formulations (1-4) used Lactose monohydrate as filler, whereas, Formulations (5 and 6) used corn starch and MCC as filler. In Formulations (7-10) Di-calcium phosphate dehydrates was used as filler.

The impact of the type of the granulating solvents on tablet disintegration and drug release under both fasting and viscous conditions was assessed. Two types of solvents were used for granulation: water and ethanol. In this work, formulations with odd numbers (1, 3, 5 , 7, 9), used purified water as granulating solvent while formulations holding even numbers (2, 4, 6, 8, 10) had adopted ethanol as the granulating solvent.

Furthermore, the effect of mode of incorporation of the disintegrants on tablet disintegration using extra granular and intragranular methods was evaluated.

2.2 Instrument and materials

2.2.1 Materials

API:

Paracetamol (USP) – Hubei Jiheng Pharmaceuticals

Excipients:

Lactose Monohydrate 200 mesh (EP) – Maybi

Corn starch (USP) – Zhongbao chenicals Co

Microcrystalline cellulose (EP) – JRS Pharma

Di calcium phosphate (EP) – Sudeep Pharma

PVP K30 (EP) – BTC chemical distribution

SSG (Sodium Starch Glycolate) (EP) – DFE Pharma

Mg. Stearate (EP) – Faci asia pacific

Purified water (EP) – SAMA Pharmaceuticals Co.

Alcohol (Ethanol) (USP)

HPMC

2.2.2 Instruments

Equipment's: heater and magnetic stirrer, weighting balance (RADWAG), particle size analyzer, Oven, pH meter, Spectrophotometer, (Labindio) Dissolution test Apparatus: (DS8000), Digital Disintegration test Apparatus (micro process based) (VEEGO), Compression machine, vernier caliper (Insize), Hardness tester (Thermonic), Karl Fischer

2.3 Formulation preparation

2.3.1 Formulations (1 and 2)

Formulations (1 and 2) were prepared using wet granulation technique. The compositions of the formulations are shown in Table 1. Formulation 1 and 2 were prepared using Paracetamol as active ingredient, Lactose monohydrate 200 mesh as diluent, SSG as intra granulator agent and water as the granulating solvent, whereas formulation 2 was prepared by the same procedure of formulation 1 but utilized ethanol as solvent for granulation.

Paracetamol (Paracetamol), Lactose Monohydrate 200 mesh and sodium starch glycolate were sieved through mesh number 30. The required amounts were weighted and mixed together before granulation and lubrication. Wet granulation was processed manually, because of the extremely low quantities of powder that would be lost if a rapid mixer granulator would be used.

Water was used as the granulating solvent; about 160 ml of water was used for preparing 1000 tablets. Povidone K30, was added to the purified water and mixed vigorously to dissolve all Povidone's particles. The granulating binder solution was added gradually over the powder, and by hands, powder and solvent were continuously rubbed to the level the paste became sufficiently wet and formed as small coagulated masse which can be easily cracked.

The cracked coagulated mass or paste were allowed to pass through mesh number 18, the wet granules were evenly sprinkled over the polyethylene bags with a very careful hand passing over them after which they were placed on a tray covered in an aluminum foil and placed in the oven to dry. The temperature was set at 45 °C for the first 90 minutes, after which it was again set to drop to 30 °C for another 10 hours.

Every three hours, a Loss on Drying (LOD) test was conducted to ensure that the minimum % is reached which ranges 1.8-2.2% that tells us the powder can be sent to be compressed securely and with the least possible issues.

Prior to the compression process, the granules were lubricated using a weighted amount of magnesium stearate that was passed over mesh number 60 and then sprinkled over the granules. The double polyethylene bag was then flipped repeatedly for around 4 minutes to thoroughly blend the granules with magnesium stearate.

All granules were transferred to compressor funnel and compressed using 12 mm Bi concave tooling round punch. During the compression process, tablet's weight (700 mg ±5%) and hardness (90 N ±10 N) were constantly monitored.

Formula 2 was prepared by the identical procedure used to formulate formula 1. Except in the concept of Granulating solvent, where formula 2 has utilized ethanol in the same volume of what was used in formula 1 which is 160 ml. however the weight was different owing to Ethanol’s less density than water.

Table 1

Composition of the Formulations (1-4)

Composition	Formula 1 Amount (mg/tablet)	Formula 2 Amount (mg/tablet)	Formula 3 Amount (mg/tablet)	Formula 4 Amount (mg/tablet)
Acetoamiophen	325 mg (46.43%)	325 mg (46.43%)	325 mg (46.43%)	325 mg (46.43%)
Lactose Monohydrate	312 mg (44.57%)	312 mg (44.57%)	312 mg (44.57%)	312 mg (44.57%)
PVP K30	35 mg (5%)	35 mg (5%)	35 mg (5%)	35 mg (5%)
Sodium Starch Glycolate)	21 mg (3%) Intra granulating	21 mg (3%) Intra Granulating	21 mg (3%) Extra Granulating	21 mg (3%) Extra granulating
Mg. Stearate	7 mg (1%)	7 mg (1%)	7 mg (1%)	7 mg (1%)
Purified water	160 mg	----	160 mg	-------
Alcohol (Ethanol)	-----	126.24 mg	-----	126.24 mg

*Batch size of Formula (1 and 2) = 1000 Tablets per each formula

*Batch size of Formula (3 and 4) = 500 Tablets per each formula

2.3.2 Formulations (3 and 4)

All of the raw materials used in formulas 3 and 4 are the same as those used in formulas 1 and 2, with the exception of the fact that sodium starch glycolate (SSG) was used as an extra granulator agent rather than as an intra- granulator agent in formula 1 and 2. Other than that, the granulating solvent used in formula 3 was purified water, whereas formula 4 has utilized ethanol.

In this study, formulations with odd numbers used purified water as granulating solvent, while in formulations with even numbers ethanol was used as granulating solvent. Thus, the weighted amounts of mixed powdered Paracetamol (Paracetamol) and lactose monohydrate 200 mesh that had previously been passed through mesh number 30 were

arranged over a polyethylene plastic bag and then binder solution was added gradually until forming wet paste that felt like small clumps.

Consequently, all clumps are passed through mesh number 18 and placed into the oven to dry using the same method as that used to dry formula 1 granules or left to be dried on room temperature in case of formula 4 which had utilized ethanol as granulating solvent.

The dried granules were mixed with SSG by turning a double polyethylene bag in different directions for 3 minutes. Mg stearate was then added and the process repeated in the same manner.

The disintegrant (SSG) should be added first, followed by Mg stearate, to guarantee the same contact of angel of granules at the moment of compression. On the other hand, if lubricant is applied first, there is a considerable possibility of high risk of changing the contact angel.

All granules were moved to the compressor machine's funnel, where they were compacted using a 12mm bi concave tooling round punch. Compressed tablets that met the desired physical specifications were then collected into the double polyethylene bags and labeled appropriately.

2.3.3 Formulations (5 and 6)

In order to determine the potential effect of the type of filler (swallow able and insoluble), formulations (5 and 6) were prepared using corn starch and MCC as diluent instead of lactose monohydrate which was already used in formulations (1-4) as shown in table 2.

The ingredients in batch formula 6 were identical to those in formula 5, with the exception of the granulating solvent, which was the only difference. The binder povidone K30 was combined with water in the case of formula 5, whereas ethanol was used in formula 6. As it is clear in table 2, ethanol was used in formula 6 in a quantity of 75.74 g, which is equal to 96 ml since ethanol has a density of 0.789g/ml.

Table 2

Composition of the Formulation (5, 6)

Composition	Formula 5 Amount (mg/tablet)	Formula 6 Amount (mg/tablet)
Paracetamol	325 mg (46.4%)	325 mg (46.4%)
Corn starch	111mg (16.8%)	111mg (16.8%)
MCC	165 mg (25.0%)	165 mg (25.0%)
PVP K30	33 mg (5.0%)	33 mg (5.0%)
SSG – Primojel	19.8 mg (3.0%)	19.8 mg (3.0%)
Mg. Stearate	6.6 mg (1%)	6.6 mg (1%)
Purified water	160	….
Alcohol (Ethanol)	-----	126.24 mg
*Batch size of Formula (5 and 6) = 600 Tablets per each formula		

After the addition of Paracetamol, corn starch, MCC, and finally SSG in their specified weighted amounts, the mixed powder had indeed passed over mesh number 30. After which, the binder solution was slowly and gradually poured over the mixed powders and, the wet granulation technique had just begun.

All lubricated granules were moved to the compressor machine's funnel, where they were compacted using a 12mm bi concave tooling round punch.

Note: all drying and lubrication methods are as same as for previous formulas.

2.3.4 Formulations (7-10)

Formulations (7 and 8) were prepared using Di-calcium phosphate dihydrate (non-swallowable and insoluble filler) to determine the effect of the nature of filler on tablet disintegration in viscous media.

The ingredients in batch formula 7 are identical to those in formula 8 and in the same way, the ingredients in batch formula 9 are identical to those in formula 10, with the only exception is the type of the granulating solvent. As shown in table 3, water was used as solvent in formula of odd numbers; on the other hand ethanol was used as solvent in formula of even numbers.

Formulations (7, 8) were identical in composition to formula 1 and 2, with the difference that in formulas 7 and 8, lactose monohydrate was substituted with di calcium phosphate in the amounts shown in table 3.

In formulas 9 and 10, Paracetamol was substituted for Lactose Monohydrate. Formulas 9 and 10 were placebo formulas to check how really API has a potential impact on both tablet disintegration and dissolution.

All remaining procedures including formulations, mixing, drying, lubrication and compression were totally same as done for previous formulas.

Table 3

Composition of the Formulations (7, 8, 9 and 10)

Composition	Formula 7 Amount (mg/tablet)	Formula 8 Amount (mg/tablet)	Formula 9 Amount (mg/tablet)	Formula 10 Amount (mg/tablet)
Acetoamiophen	325 mg (46.43%)	325 mg (46.43%)	------	-------
Lactose Monohydrate 200 mesh	-----	-------	325 mg (46.43%)	325 mg (46.43%)
Di – calcium phosphate di hydrate	312 mg (44.57%)	312 mg (44.57%)	312 mg (44.57%)	312 mg (44.57%)
PVP K30	35 mg (5%)	35 mg (5%)	35 mg (5%)	35 mg (5%)
Sodium Starch Glycolate)	21 mg (3%)	21 mg (3%)	21 mg (3%)	21 mg (3%)
Mg. Stearate	7 mg (1%)	7 mg (1%)	7 mg (1%)	7 mg (1%)
Purified water	160 mg	----	160 mg	-------
Alcohol (Ethanol)	-----	126.24 mg	-----	126.24 mg

* Batch size for formulas (7,8,9 and 10) = 500 Tablets per each formula

2.4 Media Composition

2.4.1 Media Simulating the Fasted State

A modified simulated gastric fluid was used to simulate the fasting states. This medium consists of 0.01 M HCl with the ionic strength adjusted to 0.1 M with NaCl.

2.4.2 Media Simulating the Fed State

HPMC E4M **s**olution (1.4%) wa**s** **s**hown to closely simulate the postprandial viscosity after ingestion of standard FDA meal.

Simulated fed state medium was prepared by adding 14 grams of HPMC gradually in 700 ml of preheated water to 80 C while stirring with a magnetic stirrer.

There is a substantial possibility of clump formation if all 14 grams HPMC are applied at once. The temperature of the hot plate is adjusted to drop to 45 °C. After that, 50 ml of distilled water containing 1.805gram (22 mM) sodium acetate was poured over the solution with continuous stirring.

1.6 ml (28mM) acetic acid was added with constant pH adjustments until the pH was confirmed to be in the range of 4.45 to 4.55. Finally, the volume was made up to 1000 ml with distilled water and stirring was continued for 24 hours getting a translucent dispersion at the end.

2.4.3 Physical Tests

The prepared tablets were evaluated for their thickness, weight uniformity, friability and hardness. Twenty tablets from each formula were collected to examine the weight of the tablets, then, from the already weighed 20 tablets, 10 tablets were randomly chosen to check the thickness and diameter, and last, these 10 tablets are broken as a consequence of checking the force required to break them into parts (hardness test)

2.5 Disintegration Studies

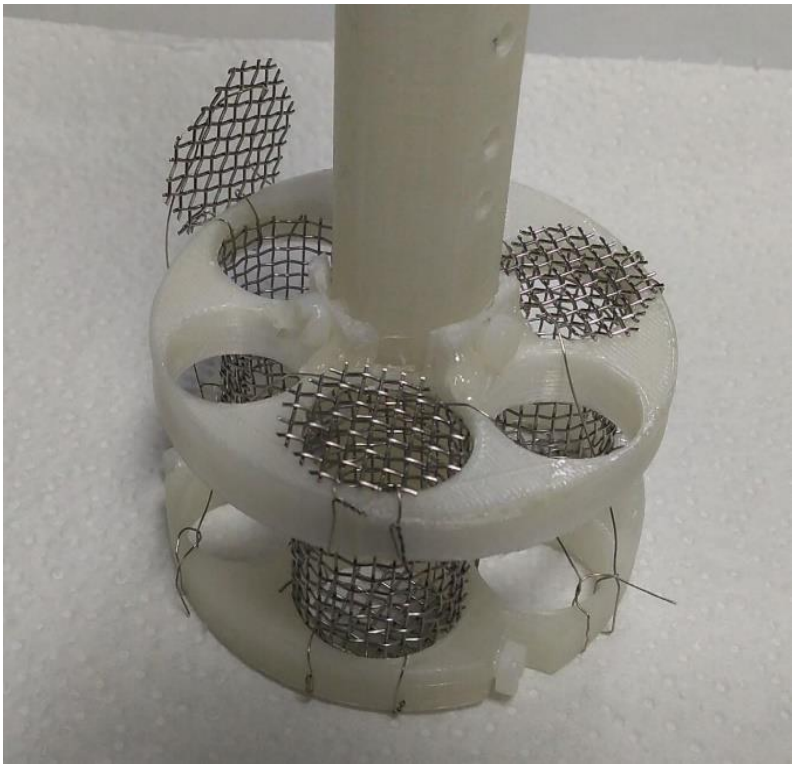
Disintegration studies were carried out in viscous and non-viscous media using a tablet Digital Disintegration test Apparatus (micro process based) (VEEGO) in an attempt to assess the effect of media viscosity on the disintegration rate and behavior of the different formulations. The disintegration test (USP without disks) was carried out in 800 ml of the

media at 37ºC using six tablets, one per vessel, for each test (Figure 2). The disintegration times are given as mean ± standard deviation.

The disintegration study was performed in two types of media: 0.01 M HCl was used as reference test media, corresponding to the fasting state, whereas, and 1.4% HPMC E4M aqueous solution was used to simulate the fed state.

Figure 2

the disintegration apparatus used to hold tablets in viscous medium



2.6 Dissolution Studies

The dissolution study of all the different formulations in Fasting and viscous media was performed in the rotating paddle apparatus II (DS8000) using 900 ml of media at 50 rpm for 45 minutes.

Five ml sample were withdrawn and filtered using 0.45 µm filtration membranes. The filtrated samples were then diluted and analyzed for the amount of Paracetamol dissolved by spectrophotometric ally (VWR UV 6300-PC) at a wavelength of 242 nm.

The dissolution samples were pooled with three tablets per experiment. The results are given as %release of the total dose

Standard preparation was being processed by Dissolving an accurately weighed amount of paracetamol equivalent to 22.22 mg of dry base in 100 ml Dissolution medium. And then the dissolved solution was Diluted by adding 5 ml of this solution to 100 ml with dissolution medium. (Conc. 0.01111 mg/ml)

Procedure: Determine the amount of Paracetamol by withdrawing 3.1 ml dissolved and diluted in 100 ml of dissolution media, and by employing UV absorption at the wavelength of maximum absorbance at about 243 nm on test preparation, in comparison with a Standard solution.

$$\% \text{ Release} = \left(\left(\frac{\text{At}}{\text{As}}\right) \times \left(\frac{\text{Cs}}{\text{Ct}}\right)\right) \times \text{F} \times 100 \quad (1)$$

In which:

At = Absorbance for test solution.

As= Absorbance for standard solution.

Cs= Concentration of standard solution in mg/ml.

Ct= Concentration of test solution in mg/ml.

F = Correction Factor

- Average dissolution profile = (Sum Av of all 6 tablets/6)

Tolerances: Not less than 80% (Q) of the labeled amount of Paracetamol is dissolved in 30 minutes.

Chapter Three

Results

This section deals with all results achieved throughout the work dedicated for thesis:

3.1 Physical Results

The physical properties of the ten formulations are presented in Table 4. The prepared tablets were evaluated for average weight, thickness, diameter and hardness. The target values for the different formulas were: (thickness: 6.0 mm± 2 mm, weight: 700 mg ± 5%, diameter of tablets: 12.0 mm ± 1 mm, and range of hardness of tablets: (80-120) N).

3.1.1 Physical Results of formula 1 and 2

Formula 1 and 2 have the same composition but manufactured with different granulating solvent). The results were achieved optimally as given in table 4. However, tablets hardness in formula 2 was higher than in formula 1, possibly as a result of the fact that all of the ethanol's granulating solvent was evaporated before compression as opposed to water, where only 1% to 2% is left, making it easier to break the tablets.

3.1.2 Physical Results of formula 3 and 4

The target values for physical parameters of formulas 3 and 4 were set in a way to be the same as those set of formulas 1 and 2, because of the fact that all ingredients in these formulas 3 and 4 are the same as those used in formula 1 and 2, the only exception was mode of incorporation of the super disintegration agent SSG, , from being internally used in formula 1 and 2 to externally in formula 3 and 4 during the granulation process. The result showed that the method of incorporation of super disintegrant has a potential impact on the physical parameter, hardness.

Formulations 3 and 4 containing SSG as extra granular disintegrant have higher crushing strength compared to formula 1 and 2, where the super disintegrant was incorporated internally.

3.1.3 The Physical properties of formula 5 and 6

In formula 5 and 6 Target values were established (thickness: 5.9 mm± 2 mm, weight: 700 mg ± 5%, diameter of tablets: 12.0 mm ± 1 mm, and range of hardness of tablets:

(110-140) N), thickness was lower than the value set for the previous four formulas because of high density of MCC and Corn starch, and the results were achieved in the specified ranges. A small discrimination was noticed between hardness results from both formulas, where the average of hardness in formula 5 was 122 N and 132 N in formula 6 which again believed to be due to the type of granulating solvent, ethanol my evaporated before compression as opposed to water, where only 1% to 2% is left, making it easier to break the tablets.

3.1.4 Physical Results of formula 7, 8, 9 and 10

The first and most parameter set and taken as most priority for formulas 7 and 8 was thickness, as Dicalcium phosphate had replaced Lactose monohydrate 200 mesh in the formula, The presence of this substance reduced the real volume of the tablet, which was reduced by calculating h from the equation as the proportional is direct, moreover in formula 9 and 10 thickness was further decreased in the placebo formula, indeed it was the reason behind omitting paracetamol and substituted it by DCP.

As the P.value of Dicalcuium phosphate is greater than that of paracetamol, this reflects on a further drop in the real volume of the formula, and this reflection has caused (thickness = h) to reduce further. Other physical factors for the last four formulas were established in a variety of ranges and achieved via in-process tracking while compressing all tablets.

Table 4

Results of the Physical Parameters of the different formulations (1-10)

Specification	Results									
	Formula 1		**Formula 2**		**Formula 3**		**Formula 4**		**Formula 5**	
	Average	S.D	Average	S.D	Average	S.D	Average	S.D	Average	S.D
Thickness (mm)	6.12	0.12	6.173	0.01	5.93	0.07	6.098	0.02	5.932	70.0
Weight of 20 tablets (mg)	707.8	8.07	708.82	6.2	691.05	9.12	688.095	8.11	675.635	5.58
Diameter (mm)	12.06	0.004	12.06	0.01	12.099	0.02	12.077	0.01	12.103	0.01
Hardness (N)	94.8	6.13	106.5	7.4	127.9	4.2	130.8	5.63	121.6	3.66
Specification	**Formula 6**		**Formula 7**		**Formula 8**		**Formula 9**		**Formula 10**	
	Average	S.D	Average	S.D	Average	S.D	Average	S.D	Average	S.D
Thickness (mm)	5.869	0.031	5.584	0.010	5.368	0.032	5.087	0.041	4.98	0.024
Weight of 20 tablets (mg)	669.555	2.851	735.875	6.728	699.8	9.567	704.055	7.309	681.24	4.792
Diameter (mm)	12.062	0.02	12.126	0.02	12.072	0.019	12.069	0.015	12.085	0.03
Hardness (N)	132.1	3.45	159.5	5.78	132.9	10.86	103.2	6.18	107	3.62

3.2 Disintegration time studies

The average disintegration times for all tested formulations were examined under both fasting and fed states (Tables 5, 6, 7). The effect of process variables of wet granulations on tablet disintegration was investigated.

Understanding of the effect of formulations parameters on tablet disintegration will help in developing formulations that avoid food effect under fed condition.

3.2.1 The effect of the type of solvent of granulation on tablet disintegration

In order to investigate the effect of the granulating solvent on tablet disintegration, water and alcohol were employed for wet granulation. Formulations with odd numbers (Formulas 1, 3, 5, 7, 9) were prepared by using alcohol as solvent of granulation, While Formulations holding even number (Formulas 2, 4, 6, 8, 10) were prepared by using water as a granulation solvent. The result showed that the type of solvent of granulation has a crucial role in modulating disintegration time of all the formulations (except formulations 5 and 6) where the role of granulating solvent in these formulas was almost negligible.

Formulations prepared by using alcohol as a granulating solvent showed shorter disintegration times compared to formulations using water as a granulation solvent (even number) in both fasting and fed states.

- **isintegration of formula 1 and 2:**
  In simulated fasted state, the average disintegration time for formula 1 was 11:31 minutes, however disintegration time for formula 2 was relatively fast (2:97 minutes).
  In simulated fed state; the average time for disintegration for formula 1 was quietly lengthy 41:26 minutes, whereas formula 2 required 11:46 minutes to complete disintegration on the same prepared medium.

- **isintegration of formula 3 and 4:**
  The average disintegration time for formula 4 in simulated fasted medium was (5:93 minutes) which was relatively faster than formula 3 (10:87 minutes).
  In simulated fed state; the average time for disintegration for formula 4 was quietly lengthy 46 minutes, whereas the time of dintegration of formula 3 was lengther and required 56.83 minutes to complete disintegration on the same prepared medium.

- **Disintegration of formula 5 and 6:**
  The effect of granulating solvent was almost negligible in these formulas once comparing them with each other on both fasting and fed media, the results were mostly same for formula 5 and 6. The impact of granulating solvent was seen in all prior and subsequent formulations, with even formulas or those using ethanol as a granulating solvent accelerating disintegration, howevr odd formulas or those using water as a granulating solvent have been seen slower.

- **isintegration of formula 7 and 8:**

  In non viscous medium, the average disintegration time for formula 7 was 4.4 minutes, whereas , formultion 8 had completely disintegrated in less than 1 min. In fed viscous medium, formultion 7 required 37.46 minutes to complete disintegration, where formultion 8 required 34.07 minutes.

Table 5

Disintegration time for Formulations (1-4) under simulated fasted and fed condition

Disintegration time (Hr: min:sec)	Tab 1	Tab 2	Tab 3	Tab 4	Tab 5	Tab 6	Av	S.D
	Results of formula 1							
Fasting	8:41	11:00	11:36	11:58	12:18	12:20	11.31	1.26
Fed	40:01	41:02	41:02	41:49	41:49	41:49	41.26	0.66
	Results of formula 2							
Fasting	1:33	1:37	2:51	2:52	2:58	3:00	2.97	1.42
Fed	10:17	10:24	10:55	11:38	12:46	12:46	11.46	1.02
	Results of formula 3							
Fasting	10:10	10:53	10:55	10:55	10:59	11:24	10.87	0.36
Fed	49:34	52:14	54:18	55:59	1:01:22	1:7:31	56.83	5.99
	Results of formula 4							
Fasting	5:41	5:46	5:51	5:53	6:1	6:24	5.93	0.23
Fed	44:25	45:00	46:12	46:12	47:06	48:09	46.18	1.24

Table 6

Disintegration time for Formulations (5 and 6) under simulated fasted and fed condition

Disintegration time (Hr: min:sec)	Results of formula 5							
	Tab 1	Tab 2	Tab 3	Tab 4	Tab 5	Tab 6	Av	S.D
Fasting	0.35	0.35	0.35	0.35	0.35	0.35	0.35	00
Fed	3:25:0	3:27:0	3:30:0	3:34:0	3:40:0	3:48:0	3:34:0	7.94
	Results of formula 6							
Fasting	0.40	0.40	0.40	0.40	0.40	0.40	0.40	00
Fed	3:24:0	3:28:0	3:32:0	3:41:0	3:44:0	3:46:0	3:35:0	8.29

Table 7

Disintegration time for Formulations (7-10) under simulated fasted and fed condition

Disintegration time (Hr: min:sec)	Results of formula 7							
	Tab 1	Tab 2	Tab 3	Tab 4	Tab 5	Tab 6	Av	S.D
Fasting	4:07	4:09	4:13	4:34	4:37	4:39	4.39	0.23
Fed	35:11	36:09	36:55	37:18	39:28	39:44	37.46	1.65
	Results of formula 8							
Fasting	0:33	0:35	0:41	1:12	1:15	1:20	0.93	0.33
Fed	32:11	33:26	34:09	34:40	34:59	35.01	34.07	1.01
	Results of formula 9							
Fasting	4:00	4:36	4:43	4:47	4:49	5:07	4.67	0.34
Fed	24:00	24:13	24:13	24:30	24:43	24:43	24.40	0.27
	Results of formula 10							
Fasting	2:26	2:27	2:28	2:30	2:30	2:31	2.48	0.03
Fed	21:16	21:30	21:30	21:30	21:55	21:55	21.60	0.24

3.2.2 The effect of mode of incorporation of the superdisintegrant

To study the effect of method of incorporation of the superdisintegrant (SSG) on disintegration time, the superdisintegrant SSG was incorporated by extra granular, and intragranular modes, in wet granulation techniques. Formulas 3 and 4 contain extra granular disintegrant, where formula 1 and 2 contain intra- granular disintegrant. Formula 3 and 4 were completely identical to formulas 1 and 2 in terms of their compositions, respectively.

In an attempt to understand the impact of the mode of incorporation of the super disintegrant (SSG) on disintegration**,** formulations manufactured with the same granulating solvent were compared. Therefore, the findings were compared in the following sequences: first, comparing the outcomes of formulas 1 and 3, which were both formulated using water, and formulas 2 and 4, which used ethanol as the granulating solvent.

The results for the effect of mode of incorporation of the superdisintegrant (SSG) on the disintegration time represented in table 5. The result shows longer disintegration time when SSG was incorporated extragranularly compared to the intra-granular counterparts.

Applying SSG externally result in an increase in the time the tablet took to disintegrate in fasting medium from an average of 2 minutes (formula 2) to 5 minutes (formula 4). Moreover, in media simulating Fed state, the average of disintegration time for formula 2 was almost 11 minutes, on the other hand the average of disintegration time for formula 4 was 46 minutes.

In the same manner, the disintegration times for formula 1 and 3 were compared. In the fasting state, formula 1 and formula 3 have roughly the same disintegration time, but under fed condition, formula 3 needed 16 minutes (extra time) to complete disintegration compared to the time formula 1 needed.

3.2.3 The effect of type of filler on tablet disintegration

Fillers comprise the major proportion of the tablet. In this study, the impact of filler type on the disintegration time was investigated. Formulations containing different type of fillers were prepared. Formulations 1-4 used lactose monohydrate which classified as

soluble filler, where Formulations 5 and 6 were prepared using corn starch and MCC to test their swellability and insolubility features on the behavior of tablet disintegrations. Formulations 7 and 8 used dibasic calcium phosphate (DCP) due to its aqueous insolubility.

To study the effect of filler type on tablet disintegration, formulations prepared with the same granulating solvent and the same mode of disintegrant incorporation were compared. As mentioned before, formulations holding odd numbers (1, 3, 5, 7, 9) have been formulated with water, while formulas holding even numbers (2, 4, 6, 8, 10) were formulated with ethanol.

Figure 3 (a, b) shows the disintegration times for odd formulas (1, 3, 5, 7, and 9) in both Fasting and fed states. In media simulating fasted conditions: formulation 5 containing combinations of starch and MCC gave the shortest disintegration time (less than 1 minute was required to complete disintegration). However, Lactose based Formulations (1 and 3) showed the longest disintegration time (11 minute).

Formulations employed Di-calcium phosphate in their composition, as an excipient in formula 7 and as a placebo by replacing the active ingredient in formula 9 displayed largely the same disintegration time behavior on fasting condition (4.5 minute).

Filler nature was also found to have significant effects on tablet disintegration in fed state. MCC based formulations (5) showed very slow disintegration behavior, taking 3 hours and 35 minutes. However, the use of dibasic calcium phosphate (DCP) diluent resulted in the shortest disintegration times compared to other diluents used in fed conditions.

Figure 4 (a, b) show the disintegration times for even formulas (2, 4, 6, 8, and 10) in both Fasting and fed states. It is clear that formula 6 exhibited the quickest disintegration in medium simulating fasting situation; however, in viscous fluids, it demonstrated the slowest manner of disintegration.

Figure 3.A

Average Disintegration time for odd formulas on Fasting state

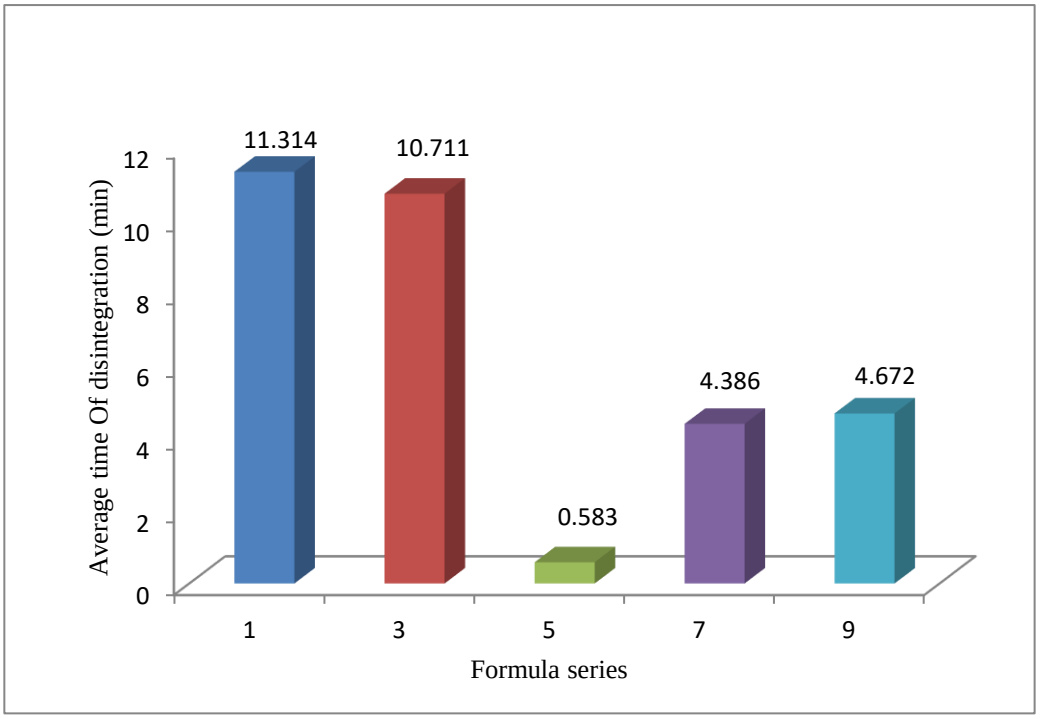


Figure 3.B

Average Disintegration time for odd formulas on Fed state

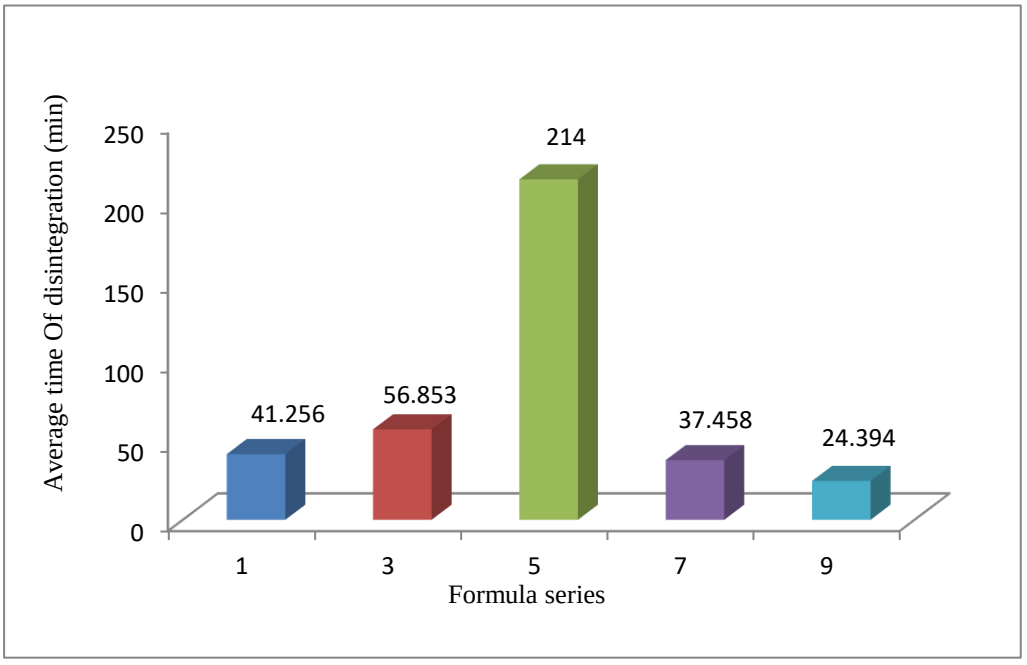


Figure 4 (A&B) show the disintegration times for even formulas (2, 4, 6, 8, and 10) in both fasting and fed states. In these formulas, the granulating solvent was the same in all, which was ethanol.

In media simulating Fasting state, it is clear that formulations 6 containing MCC gave the shortest disintegration time, among all formulations tested. Formulation 8 used Dicalcium phosphate as diluent underwent rapid disintegration (less than 1 minute). However, Lactose based formulations (2, 4, 10) showed longer disintegration times. Formula 4 was the slowest formula in which SSG was integrated exteriorly. Interestingly, disintegration times of formulations 2 were not much different from that of formulations 10 (Figure - 4B). Both of them contained lactose monohydrate: formulations 2 used lactose as diluent, where formulation 10 was placebo tablet with no active ingredient. Both lactose and DCP were utilized as diluents. The disintegration results showed that lactose effect was the predominant.

In fed viscous conditions, formula 6 (MCC) demonstrated the slowest manner of disintegration in viscous fluids. Formula 8 used DCP showed shorter disintegration time compared to (MCC). Surprisingly, the use of lactose monohydrate diluent result in the shortest disintegration times in fed conditions which is in contrast to its behavior in fasting conditions. Formula 2 was the fastest formula to disintegrate in fed medium, but underwent low disintegration in fasting medium.

The disintegration time for Formula 10, which contained both lactose and DCP as diluents, was in between that for formulas containing either lactose or DCP alone.

Figure 4.A

Average Disintegration time for even formulas (2, 4, 6, 8,10) on Fasting state

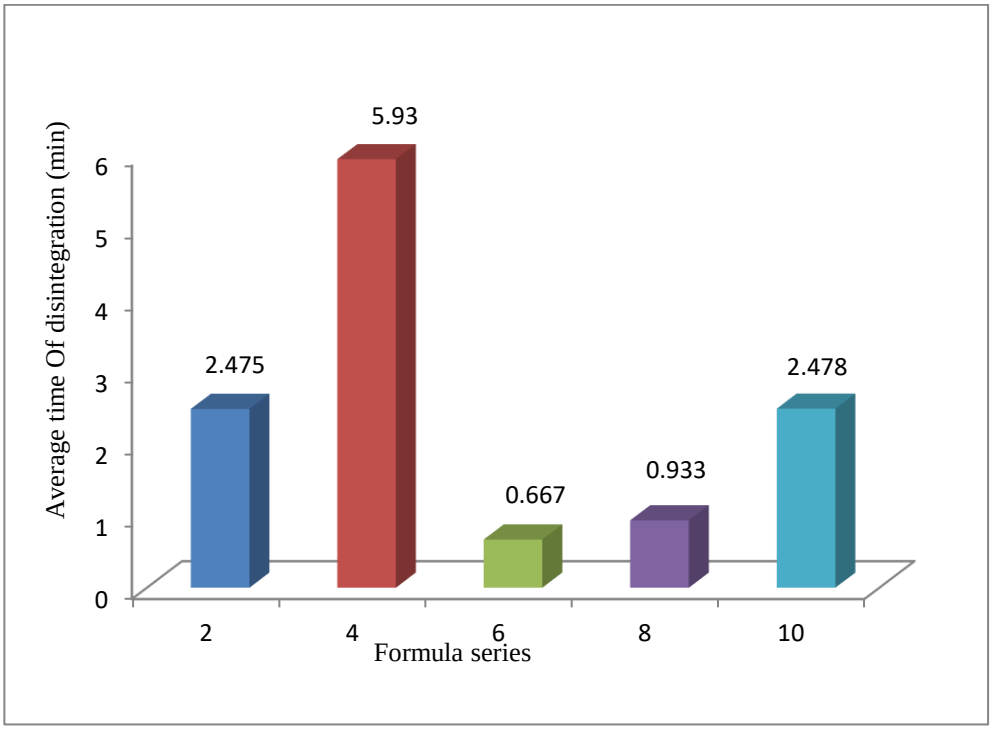


Figure 4.B

Average Disintegration time for even formulas (2, 4, 6, 8,10) on Fed state

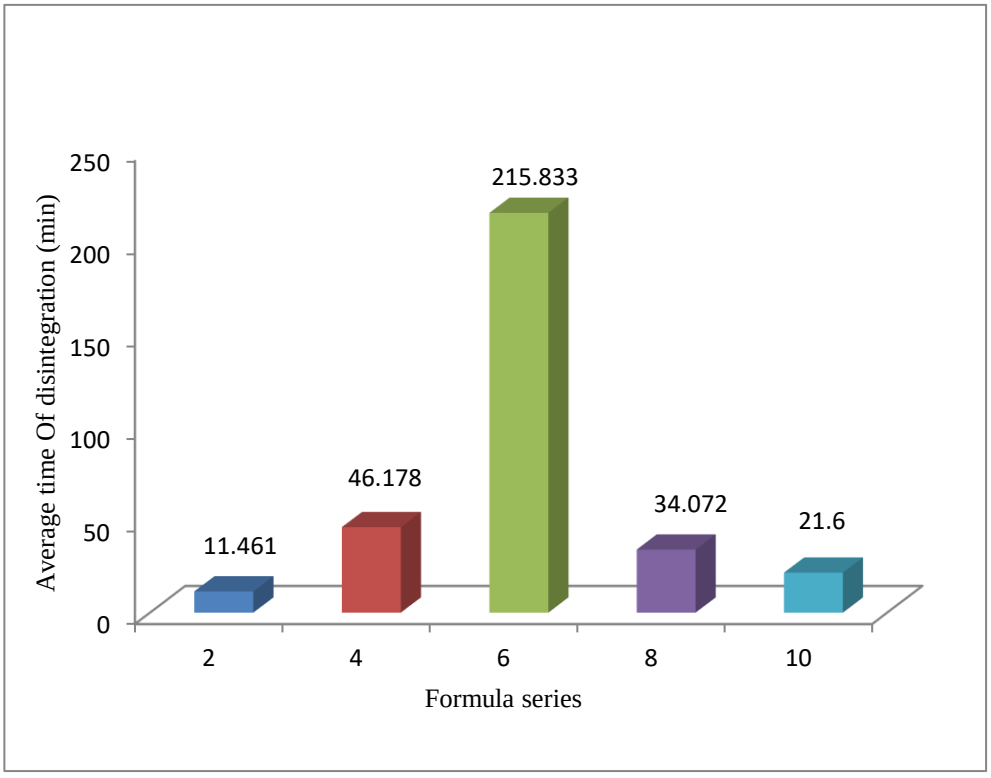
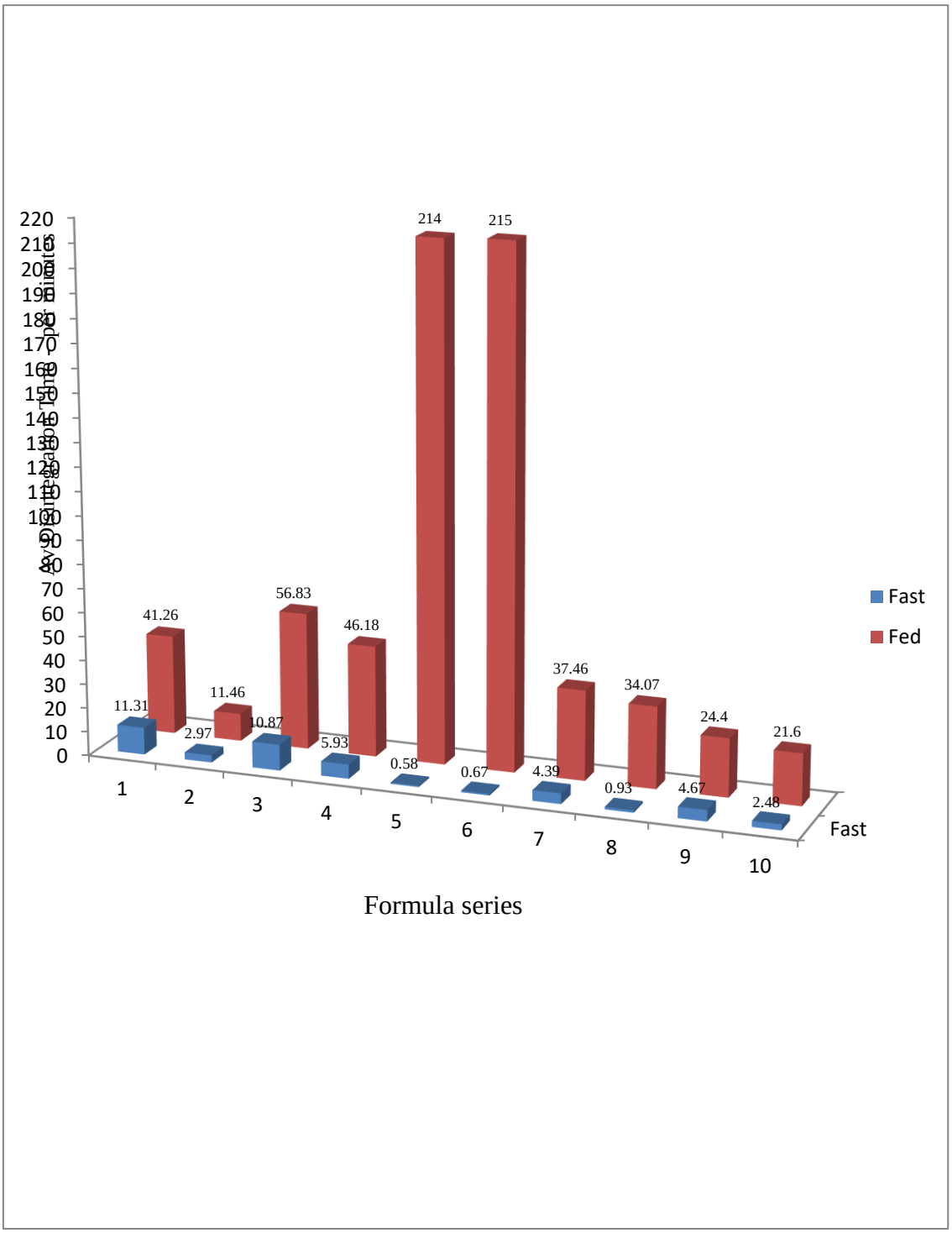


Figure 5

Comparative 3D Columns for all results of Disintegration time for all formulas simulating both Fasting and Fed state



3.3 Dissolution Results

In this part, Dissolution profiles for the formulations 1, 2, 3, and 4 were evaluated in both fasting and fed states (Table 8). The effect of the processing parameters of wet granulation technique on drug release was investigated: The effects of mode of incorporation of the superdisintegrant as well as the effect of type of solvent of granulation on dissolution were evaluated.

3.3.1 The effect of the type of solvent of granulation on drug Dissolution

In this study, the effect of type of the granulating solvent on tablet drug dissolution was investigated in both fasting and fed states. water and alcohol were used as solvents for wet granulation in formulations holding odd and even number, respectively.

Dissolution profiles for Formulations having similar composition but differing in the type of the granulating solvent were compared together.

- **ormulations (1, 2)**

  When tested under non-viscous conditions, formulation 2 showed very rapid dissolution with more than 85 % of API was released within the first 5 minutes time interval. On the other hand, the dissolution results for formula 1, indicated that only 38% of the medication was released at 5minute point, 77% of the medication was released at the time point 10 minutes and It took formula 1 about 15 minutes to undergo complete drug release.

  In simulated fasted state, the release rates from both formulations complied with the criterion for “very rapid dissolution” (i. e. more than 85 % drug dissolved in 15 min).

  In viscous fed media, drug release from the formulations was found to be slower when compared to fast conditions (Table 9): Less than 60% of drug was released within 30 minutes. Formulation 2 showed higher dissolution rates compared to formulation 1 in the early stage of drug release.

- **Formulations (3, 4)**

  When tested under fasting conditions: Formulations (3, 4) showed very similar drug release profile. Both formulations showed very rapid dissolution i.e. more than 85 % of API was released within 15 min.

Under viscous conditions, formulations 4 having alcohols granulating solvent showed better and faster dissolution profile than Formulations 3.

The results showed that the type of solvent of granulation may play a role in modulating drug release under fed states.

Formulations prepared by using alcohol as solvent of granulation showed better dissolution compared to formulations using water. Dissolution results are in line with the disintegration results.

Table 8

Cumulative percent of drug release from formula (1-4) under condition simulating Fasting State

Time (minute)	Cumulative percent of drug release			
	F1	F2	F3	F4
5	38	85	51	55
10	77	99	76	84
15	97	98	87	92
20	98	96	87	94
30	101	96	88	96
45	101	102	88	96

Table 9

Cumulative percent of drug release from formula (1-4) under condition simulating Fed State

Time (minute)	Cumulative percent of drug release			
	F1	F2	F3	F4
5	3.2	9.9	0.19	4.86
10	13.3	19.8	5.82	8.24
20	32.3	36.7	11.4	21.3
30	57.7	55.8	27.5	34.3
45	79.7	84.1	57.4	45.6
60	97.0	99.1	78.8	87.0
120	106	101.3	101.4	112.3

Figure 6.A

Comparative Dissolution curves profile for formula (1,2,3,4) in simulating Fasting State

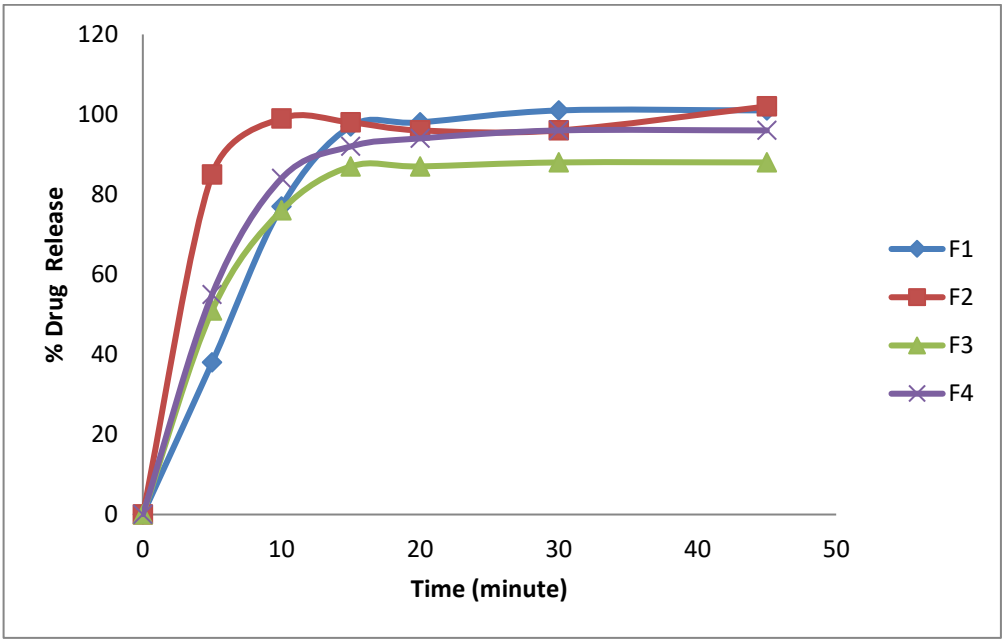
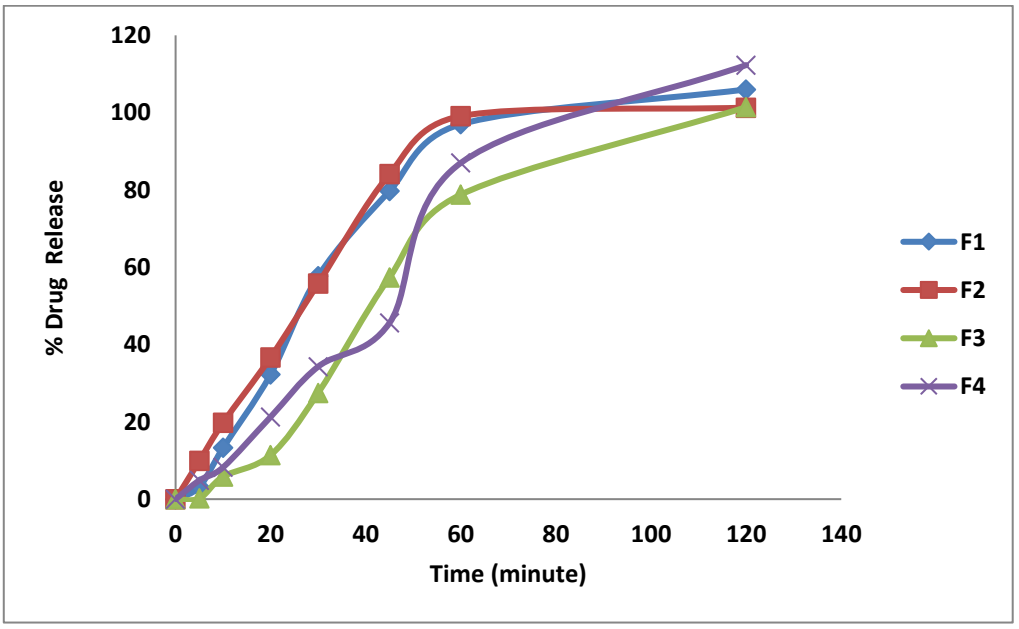


Figure 6.B

Comparative dissolution curves profile for formula (1,2,3,4) in simulating Fed State



3.3.2 The effect of mode of incorporation of the superdisintegrant

To study the effect of mode of incorporation of the superdisintegrant (SSG) on drug release properties, different formulas were prepared by incorporating SSG extra granularly, and intragranularly. Formulas 3 and 4 utilized extra granular disintegrant, where formula 1 and 2 contained intra- granular disintegrant. Formula 3 and 4 were completely identical to formulas 1 and 2 in terms of their compositions, respectively.

Drug release properties for Formulations having similar composition and formulated with the same granulating solvent, but differing in the mode of incorporation of the superdisintegrant were compared together. Therefore, the findings revealed that mode of incorporation plays crucial role on the behavior of the drug release and found in accelerating the drug release once the mod of incorporation in internally and slowing the rhythm of the release once SSG were incorporated externally.

The results for the effect of mode of incorporation of the superdisintegrant (SSG) on the Dissolution performance are shown in figure 6 (A and B).

Under viscous condition, Drug release form Formulation prepared with extra granular disintegrant was lower compared to the intra-granular counterparts.

Chapter Four

Discussion

The aim of this work was to study the effect of formulation and processing factors on drug release and tablet disintegration under fed conditions. Various formulation and processing parameters were evaluated by testing both disintegration and dissolution for different formulation under both fasting state and fed state: The potential of filler type as well as, the effects of wet granulation parameters such as the mode of incorporation of disintegrant and the type of the granulating solvent were highlighted.

This study provides deep understanding of the critical formulation and processing parameters affecting drug product performance under fed conditions, which will help to devise a formulation strategy that can minimize the viscosity, mediated negative food effects.

4.1 The effect of the type of filler

Fillers comprise the major proportion of the tablet. The impact of different types of fillers on the dissolution and disintegration rates was obvious. The fillers used in this study i.e., lactose, DCP and MCC, showed significant effect on the disintegration and dissolution times, under fasting and fed conditions.

In simulated fasted state: MCC based formulations gave rapid disintegration because of its good swelling tendencies and water imbibing properties. Where, Lactose based formulations with Paracetamol and water combination as granulating solvent gave the slowest disintegration. Probably because of lactose dissolution and recrystallization during granulation with water resulting in substantially finer pore structure.

In Simulated fed state: MCC based formulations were the worst: they needed more than 3 hours to complete disintegration under viscous media, While the swellability of MCC excipients under simulated fasted state was advantageous in disrupting the tablet, however under fed conditions, it became a disadvantage. It blocked the pores slowing down water ingress, and the slow pace of swelling allowed for stress relaxation reducing its disruptive effects on tablet integrity.

On the other hand, Lactose and DCP based formulations provide rapid dissolution under fed state, which is in contrast to the fasted state where it gave the slowest disintegration. Lactose faster disintegration in fed state is explained based on its dissolution and leaching properties providing additional pathways for medium penetration. An exception is with formulation 1 which is slower than the formulation containing DCP counterpart (Needs further investigation).

These results are in line with zaheer and langguth findings. (5,6) They reported comparable disintegration rates for lactose based tablets followed by DCP based tablets. These observations were attributed to the solubility aspect of fillers. Lactose is water soluble filler, which undergoes rapid dissolution. The dislocation of the dissolved filler particles result in an increase in tablet porosity and thereby increase the effective surface area for the API.

While DCP is hydrophilic, but insoluble, the rapid wicking of medium into the tablet occurs, with no de-aggregation of the matrix. The prolonged disintegration time for MCC-based tablets under fed conditions was attributed to the strong internal bonding among the swollen MCC particles in the tablets.

4.2 The effect of the type of solvent of granulation

The type of the granulation solvent is an important parameter controlling tablet disintegration. In this study, formulations prepared by using alcohol as solvent of granulation had shorter disintegration times compared to formulations using water in both fasting and fed states. This can be attributed to the lower surface tension of ethanol compared to water which produces granule with large pores. Previous studies have shown that granule porosity during wet granulation is influenced by the surface tension of the agglomeration liquid. (65,66)

The effect was most pronounced in Lactose based formulation (formula 2), probably because of the effect of lactose dissolution and recrystallization resulting in substantially finer pores with water (needs to be confirmed by porosimtry).

This seems contradicted by the results of the lactose-DCP formulation where the difference is also not large, but probably the presence of the more hydrophilic DCP

reduced the difference through its promotion of capillary water uptake. Little difference in the starch-MCC formulation probably due their swelling blocking pores in both cases.

These findings are in agreement with previous reports. Microcrystalline cellulose pellets produced with water alone had large disintegration time compared to when alcohol was used. These observations were attributed to the larger extent of swelling and mechanical interweaving of solvated cellulose chains of MCC particles during wet agglomeration upon using water. The type of the granulation solvent was shown to impact the mechanical and structural properties of the formulated pellets. The porosity of formulation produced with ethanol is substantially higher than those produced with water.

4.3 Effect of mode of incorporation of the superdisintegrant

The mode of inclusion of the disintegrant intra-, extra-granularly may have an impact on the disintegration behavior of a tablet. Under fasting state, the addition of SSG intra-granularly to water granulated tablets results in comparable disintegration time to the extra-granular counterparts. On the other hand, intragranular incorporation of SSG gave faster disintegration with ethanol granulated tablets. These findings are contrary to previous reports, in which the disintegration efficiency of Superdisintegrant agent used externally was more rapid than when used internally due to wetting and drying during the granulation process. Lactose dissolution and recrystallization in the presence of water could be the reason for these observations

Under fed conditions, formulation with intra-granular superdisintegrant provided faster disintegration than extra-granular, probably due to the confinement of the swelling disintegrant resulting in greater stress.

In dissolution results, the effect of the granulating solvent is weaker, being apparent only at the early timepoints. On the other hand, the disintegrant mode of incorporation effect remains strong, probably because granule deaggregation lags behind tablet disintegration.

In the light of this work, in order to develop drug products with the lowest negative food effect, lactose based formulations are recommended using alcohol solvent of granulation and intragranular mode of incorporation of super disintegrant.

These results will help in designing products the performance exhibits little sensitivity to concomitant food intake, and thus are less prone to negative effects of patient compliance issues. In addition, it could open the door for waiving fed bioequivalence studies under certain conditions, thus reducing the financial and ethical burden associated with generic product development. This will be particularly helpful to the Palestinian pharmaceutical industry, which is almost entirely generics-focused, and the costs of bioequivalence study comprise a major financial burden for this sector that struggles with the harsh economic realities imposed by the political situation.

4.4 Conclusion

Food's negative effect is a critical factor that must be taken into account by all drug manufacturers. Food my delay tablet disintegration and causes drug release to be retarded, resulting in a decrease in the quantity of medication in the systemic circulation.

Many formulations have been developed in this study to analyze and assess all conceivable parameters that have a direct influence on the behavior of tablet disintegration and drug release. Including, but not limited to, the kind of filler or diluent that makes up the majority of the tablet weight, the granulating solvent, and the way of incorporation the super disintegrant agent.

This thesis is directed towards evaluating the potential of formulation excipients such as filler type on drug bioavailability under fed condition. Filler type may have significant influence on tablet disintegration and dissolution in the presence of food. Tablets formulated using lactose and DCP showed faster dissolution and disintegration rates as compared with those formulated using MCC.

This study has also focused on the effect of the critical formulation and processing parameters on the in vitro drug product performance under viscous condition. The role of wet granulation parameters such the type of granulating solvent and mode of incorporation of disintegrant on drug release was addressed. Formulations using ethanol as granulating solvent showed faster disintegration rates when compared with those formulated using water. The addition of SSG intra-granularly results in shorter disintegration time compared to the extra-granular counterparts under fed condition

Tablets were formulated using lactose as filler, ethanol as granulating solvent, with intra granular disintegrating agent, was the least affected by food induced negative effect.

This study will help in predicting food viscosity mediated effect on drug product performance and design formulations with the aim of reducing this food-dependent effect on drug bioavailability.

List of Abbreviations

Abbreviation	Meaning
API	Active Pharmaceutical Ingredient
AUC	Area Under the Curve
BCS	Bio Pharmaceutical Classification System
BE	Bio Equivalence
BW	Bio waiver
CCS	Cross Carmillose Sodium
DC	Distribution Coefficient
DCP	Di Calcium Phosphate
DSC	Differential Scanning Calorimetry
DVS	Dynamic Vapor Sorption
ER	Extended Release
F	Bio Availability
FBD	Fluid Bed Dryer
FDA	Food and Drug Administration
GET	Gastric Emptying Time
GIT	Gastro Intestinal Tract
HPMC	Hydroxyl Propyl Methyl Cellulose
IR	Immediate Release
MCC	Microcrystalline Cellulose
MRI	Magnetic Resonance Image
QBD	Quality By Design
QC	Quality Control

R&D	Research and Development
RMG	Rapid Mixer Granulator
SLS	Sodium Lauryl Sulphate
SSG	Sodium Starch Glycolate

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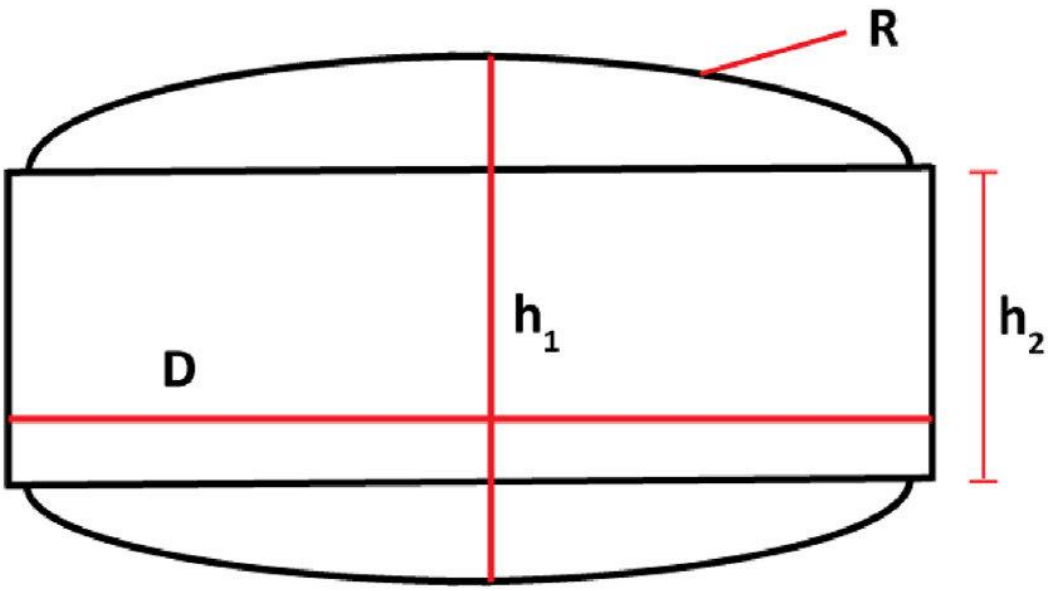
Appendices

Appendix A

Illustrating figure of the way of calculating thickness of tablet



Appendix B

CV

Zain Alabedin Y. Zanoon

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Nablus West Bank, Palestine

PROFESSIONAL SUMMARY

Proactive Regulatory Affairs Manager, possessing excellent negotiation and persuasion techniques during my visits to Palestinian MOH and Jordan JFDA. Analytical problem-solver, dedicated to pushing pharmaceutical products to market by offering 7 years of experience with high qualification.

CORE QUALIFICATIONS

- Self-motivated with positive attitude
- Team work spirit and dependable
- Ability to work under pressure and limited time
- Ability to deal with all kinds of people
- Ability to handle Problems and find solutions
- Ability to learn new concept quickly by methodical approach
- Excellent ability to interact with customers
- Excellent ability to make new relations related in business wise
- Excellent ability of Convincing others

REFERENCES

References : available upon request.

LANGUAGES

- Arabic: Native.
- English: Excellent.
- Urdu : speaking only.

EXPERIENCE

01/2020 - Current
Regulatory Affairs Manager | Nablus, West Bank
SAMA Pharmaceuticals Manufacturing Co.

04/2018 - 01/2020
Medical Representative | Nablus, West Bank
SAMA Pharmaceuticals Manufacturing Co.

09/2017 - 03/2018
Regulatory Affairs Supervisor | Nablus, West Bank
SAMA Pharmaceuticals Manufacturing Co.

02/2017 - 08/2017
Regulatory Affairs Pharmacist | Nablus, West Bank
SAMA Pharmaceuticals Manufacturing Co.

07/2016 - 01/2017
R&D Pharmacist | Nablus, West Bank
SAMA Pharmaceuticals Manufacturing Co.

01/2016 - 07/2016
QC Pharmacist | Nablus, West Bank
SAMA Pharmaceuticals Manufacturing Co.

EDUCATION

2022
Annajah National University | Nablus
Master of Pharmaceutical Sciences: Pharmaceutical Technology
I have got honored grade and first position holder with GPA: 3.65/4

2016
Sindh University | Hyderabad - Pakistan, Pakistan
Doctor of Pharmacy (Pharm.D): Pharmacy
I have got honored grade and fourth position holder with GPA: 3.84/4

2010
King Talal High School | Nablus
High secondary: Scientific stream

TRAINING AND EXHIBITIONS

- **API and route of synthesis**
  Mumbai India. 12 hours training course
- **GMP guidelines**
  Professor Bashar al Khalidi – JFDA consultant.
- **GLP (Good Laboratory Practice)**
  intensive course - Nablus West Bank (Alnnajah National University - Bio center) 6 months training course.
- **GCC (Good Clinical Practice)**
  intensive course - Nablus West Bank (Alnnajah National University - Bio center) 6 months training course.
- **Communication Skills training course**
  Nablus West Bank Chamber of Commerce and industry.
- **eCTD training course**
  Amman - Jordan.
- **Pharmacovigilance training course**
  Amman - Jordan

جـامعـــة النجاح الوطنية

كلية الدراسات العليا

تأثير اللزوجة الناتجة عن الغذاء على إذابة وتفكك الأقراص: تأثير الصيغة ومعاملات تغير العملية على الأقراص المصنعة بواسطة التحبيب الرطب

إعداد

زين العابدين زعنون

إشراف

د. أسماء رضوان

قدمت هذه الرسالة استكمالا لمتطلبات الحصول على درجة الماجستير في العلوم الصيدلانية، من كلية الدراسات العليا، في جامعة النجاح الوطنية، نابلس– فلسطين.

2023

تأثير اللزوجة الناتجة عن الغذاء على إذابة وتفكك الأقراص: تأثير الصيغة ومعاملات تغير العملية على الأقراص المصنعة بواسطة التحبيب الرطب

إعداد

زين العابدين زعنون

إشراف

د. اسماء رضوان

الملخص

قد يؤدي ارتفاع لزوجة المعدة بعد الأكل إلى تأخير تفكك الأقراص وتأخير انحلال الدواء من أشكال الدواء ذات الجرعات الصلبة، مما يؤدي إلى انخفاض كبير في التوافر الحيوي للدواء وبالتالي التأثير على الفعالية العلاجية. قد يكون هذا أمرًا بالغ الأهمية خاصة بالنسبة للأدوية التي تتطلب بداية سريعة للعمل. سيساعد الفهم العميق لمعايير المعالجة الحرجة على تفكك الأقراص وانحلال الدواء في ظل ظروف التغذية في تصميم تركيبة دوائية تتأثر بالحد الأدنى من اللزوجة بتأثيرات غذائية سلبية.

يهدف البحث الحالي إلى دراسة تأثير عوامل التركيبة والمعالجة على تفكك الأقراص وتحرر المادة الصيدلانية الفعالة في كل من حالتي الصيام والتغذية. تم دراسة تأثير أنواع مختلفة من الحشوات بتركيبات مختلفة: اللاكتوز مونوهيدرات، نشا الذرة، السليلوز دقيق التبلور، وكذلك ثنائي فوسفات فوسفات ثنائي الكالسيوم. يعتبر التحبيب الرطب خطوة تصنيع حاسمة لأشكال الجرعات الصلبة الفموية. تم تطبيق طريقة التحبيب الرطب في تحضير عشر تركيبات ذات إطلاق فوري مع استخدام الباراسيتامول كدواء نموذجي. تم تسليط الضوء على تأثيرات معاملات التحبيب الرطب مثل: طريقة دمج المادة المفككة ونوع المذيب المستخدم للتحبيب.

خلصت الدراسة إلى أن نوع الحشو وجد أنه يؤثر على تفكك الأقراص: أعطت التركيبات القائمة على السليلوز دقيق التبلور تفكيك أسرع للدواء في حالة محاكاة الصيام، لكنها كانت الأسوأ تحت الوسط اللزج.

توفر التركيبات القائمة على اللاكتوز والفوسفات ثنائي الكالسيوم تفككًا سريعًا في حالة التغذية. كان للتركيبات المحضرة باستخدام الكحول كمذيب للحبيبات أوقات تفكك أقصر مقارنة بالتركيبات التي تستخدم الماء في كل من حالة الصيام والتغذية. تؤدي إضافة الصوديوم النشا غليكولات داخل الحبيبات إلى وقت تفكك أقصر مقارنة بإضافته خارج الحبيبات تحت ظروف التغذية.

الكلمات المفتاحية: سلوك ; التفتت ; الذوبان ; الصيغة الزوجية ; حالة الصيام ; حالة الإفطار ; الصيغة الفردية