COMPARISON OF COMMERCIALLY AVAILABLE MANNITOL WITH LYOPHILIZED MANNITOL AS AN EXCIPIENT FOR A MODEL ORALLY DISINTEGRATION TABLET FORMULATION

A THESIS SUBMITTED TO THE GRADUATE SCHOOL OF HEALTH SCIENCES OF NEAR EAST UNIVERSITY

By

MOHAMMED MOHSEN ZIAD

In Partial Fulfillment of the Requirements for The Degree of Master of Science In Pharmaceutical Technology

NICOSIA, 2018

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I hereby declare that all information in this document has been obtained and presented in accordance with academic rules and ethical conduct. I also declare that, as required by these rules and conduct, I have fully cited and referenced all material and results that are not original to this work.

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ACKNOWLEDGEMENTS

"My success is only by Allah" -Quran

First and foremost, I would like to give praise and thanks to Allah the almighty for his endless blessings and for granting me the knowledge and strength to reach this milestone. It is by his permission that I am who I am today.

Secondly, I would like to thank my thesis advisor and my inspiration Asst. Prof. Dr. Metin Çelik, a professor and advisor at Near Eastern University. My completion of this thesis could not have been possible without his continuous academic guidance and support. Dr. Çelik enabled me to reach my greatest and full potential and showed me that I can accomplish my dreams.

I would also like to extend my warm thanks to the head of the Pharmaceutical Department Asst. Prof. Yıldız Özalp.

I would especially like to thank Azmi Hanoğlu, Onur Horoz, Leyla Beba and Emine Dilek Özyılmaz for their technical help, and constructive suggestions which were of tremendous help for me in accomplishing the work presented in this thesis. My thanks also go to the IMCD Company for providing most of excipients used in this study.

I would also like to acknowledge the jury members (Asst. Prof. Banu Keşanlı and Assoc. Prof. their valuable input and comments.

Finally, and most importantly, I must express my profound gratitude to my beloved father and mother for their unconditional love and support. To my loving and caring wife for her patience and continuous encouragement.

My endless appreciation to my siblings who despite their distance have always been a source of empowerment and strength for me. Also, to my closest and dearest friends, Faisal and Mazen for standing by my side during the sad and happy moments of this journey.

Mohammed Mohsen Ziad

ABSTRACT

Orally disintegrating tablets is the fast growing and highly accepted drug delivery system. In the present study, an attempt had been made to compare between a commercially available mannitol with lyophilized mannitol to develop an ODT formulation and compare tableting properties of the formulations containing freeze-dried, spray-dried, granular and powdered mannitol to prepare ODT of ascorbic acid. Mannitol was used as a filler and taste masking agent while croscarmellose sodium was used as disintegrant. In this study, direct compression technique was used to prepare tablets using microcrystalline cellulose as a binder/filler. Direct compression technique is one of the most convenient and acceptable technology for preparation of ODTs. ODT of ascorbic acid prepared with different grade of mannitol were evaluated for physical parameters such as weight variation, thickness, hardness, friability, disintegration time and palatability. The challenges encountered during formulation and compaction was related to adjustment of tablet size and hardness to achieve fast disintegrating time according to the pharmacopeia recommendations. As expected, an increase in hardness resulted a decrease in friability % and increase in disintegrating time. The optimum hardness was observed to be about 40 N. in this hardness which resulted in friability values within USP limit less than 1% and disintegrating time less than 30 sec. The results revealed that the inner pore morphology of the freeze-dried mannitol is of major significance for time of disintegrating and a formula that has sufficient mechanical strength and fast disintegrating time by using lyophilized mannitol.

Key words: Orally Disintegrating Tablets, Mannitol, Disintegration

ÖZET

Ağızda dağılan tabletler hızlı büyüyen ve kabul gören bir dozaj formudur. Bu çalışmada, ascorbic acid içeren bir ODT formülasyonu geliştirmek için ticari olarak temin edilebilen spreyle kurutulmuş, tanecikli ve toz haline getirilmiş mannitol ile dondurularak kurutulmuş mannitolkullanılmış ve buODT formülasyonların tabletleme özelliklerini karşılaştırılmıştır. Mannitol, dolgu ve tat maskeleyici maddesi olarak, kroskarmeloz sodyum'da parçalayıcı olarak kullanıldı. Tabletler, bağlayıcı / dolgu maddesi olarak mikrokristal selüloz kullanılarak ve direkt baskı tekniği hazirlanmıştır. Direkt baskı tekniği, ODT'lerin hazırlanması için en uygun, ucuz ve kabul edilebilir teknolojilerden biridir. Farklı derecelerde mannitol ile hazırlanan askorbik asitin ODT formulasyonları, ağırlık değişimi, kalınlık, sertlik, kırılganlık, disintegrasyon süresi ve tad gibi fiziksel parametreler açısından değerlendirilmiştir.

Formülasyon ve direk baskı sırasında karşılaşılan zorluklar, farmakopelere göre disintegrasyon süresi elde etmek için tablet boyutunun ve sertliğin ayarlanması ile ilgilidir. Beklendiği gibi, sertlikte bir artış, friabilite yüzdesinde bir azalmaya ve parçalanma süresinde artışa neden olmuştur. Bu çalışmada optimum sertliğin yaklaşık 40 N olduğu gözlendi; bu, USP limitinin % 1'den daha az olan friabilite değerleri ve 30 saniyeden daha az disintegrasyon süresi ile sonuçlandı. Sonuçlar, liyofilize mannitolün iç gözenek morfolojisinin, parçalanmanın zamanlaması ve liyofilize mannitol kullanılarak yeterli mekanik mukavemete ve hızlı parçalanma süresine sahip bir formül için önemli bir öneme sahip olduğunu ortaya çıkarmıştır.

Anahtar Kelimeler: Ağızda dağılan tabletler, mannitol, disintegrasyon

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SYMBOLS AND ABBREVIATION

APIs:	Active Pharmaceutical Ingredients
DC:	Direct Compression
EP:	European Pharmacopoeia
FDA:	Food and Drug Administration
GIT:	Gastric Intestine Tract
IP	International Pharmacopeia
MCC:	Micro Crystaline Cellulose
N:	Newton
ODTs:	Oral Disintegrating Tablets
OTC:	Over-The-Counter
PEG 4000:	Polyethylene Glycol 4000
S:	Second
mm:	Millimeter

CHAPTER ONE

INTRODUCTION

1.1 Orally Disintegrating Tablets:

Solid dosage forms (tablet and capsule) have wide acceptance up to 50-60% of total dosage forms. Tablet form is still one of the most popular conventional dosage forms because of accuracy, dose stability, and ease of self-administration. Tablet form is also convenient and most stable in packaging, shipping and transportation. However, many patients may find difficulty swallowing tablets, and capsules leading to medication non-compliance. Dysphagia is a frequent complication associated with a number of diseases including stroke, Parkinson's disease, age-related conditions, psychiatric patients, bedridden, uncooperative, and travelling patients. It is estimated that 50% of the population is affected by this problem which results in a high incidence of incompliance and ineffective therapy (Seager, 1998; Dobetti, 2001; Sastry et al., 2000; Pahwa et al., 2010; Bhasin et al., 2011). The Food and Drug Administration (FDA) defined Orally Disintegrating Tablets (ODTs) as "a solid dosage form containing medicinal substance or active ingredient which disintegrates rapidly usually within a matter of seconds when placed upon the tongue" and provides further recommendations to point out the primary characteristics of ODTs weight (< 500 mg) and disintegration times (< 30 seconds). These two features have great influences on the ODTs. Recently, the European Pharmacopoeia (EP 4.1, 2002) adopted the term Orodispersible Tablet as a tablet to be placed in the mouth where it disperses rapidly before swallowing and which disintegrates in less than three minutes (Stange et al., 2014). Oral solids are associated with the risk of choking or chewing and with limited dose flexibility. Pediatric patients often have trouble swallowing large tablets thus raising administration difficulties (Ivanovska et al., 2014). ODTs are the preferred choice of drug form among the pediatric and geriatric population due to the rapidness of the effectiveness they provide. Moreover, patients in all ages prefer the convenience of taking medications without water, such as (ODTs). Thus, solid dosage forms that can be dissolved or suspended in the mouth are highly desirable for the above-mentioned patient groups (Dobetti,

2000; Fu et al., 2004). In this context, ease of administration and emergency situations can be counted as main reasons for increasing indent for the ODTs all of which are supported by market studies (Bandari et al., 2008; Bhasin et al., 2011). Clinically, in some cases ODTs may improve safety and efficacy. However, there are limitations to the usage of ODTs in some cases such as patients whom suffer from Sjogren's syndrome because of their inability to produce saliva as well as patients who take anti-cholinergic medications (Bharawaj et al., 2010).

These different requirements between FDA and European Pharmacopoeia are because of the different measurement methodologies applied. In comparative, The European Pharmacopoeia does not apply mechanical stress, while The Food and Drug Administration recommendation follow the same procedure that uses for conventional tablets (Stange et al., 2014). In another study, because there was no specification concerning neither the hardness nor the friability of these kinds of tablets, the market has ODTs that disintegrate in less than one minute and more than one minute. Nevertheless, these are brittle and require specified packaging and thus higher costs (Habib et al., 2000). ODTs are also known as fast melting, quick dissolve, mouth dissolving, freeze-dried wafers, porous tablets, and rapid melting etc. They are available over the counter (OTC) and can be provided as a prescription. ODTs are innovative solid oral dosage forms that are becoming increasingly important in the pharmaceutical market. Most of the difficulties encountered during the treatment periods of swallowing tablets are related to size, surface, form, and taste (Sastry et al., 2000).

1.1.1 Drug Selection Considerations ODTs

Several criteria and requirements must be considered when selecting a drug applicant for ODT dosage forms. The ideal properties and desired characteristics necessary for the success of ODTs are known as small to moderate molecular weight, low dose drugs (preferably less than 50 mg), ability to diffuse and partition into the epithelium of the upper Gastric Intestine Tract (GIT) Ability, non-ionized in oral cavity pH 5.5-7.4, good stability in aqueous medium, good compatibility, and less sensitive to environmental circumstances (humidity and temperature). However, short half life, frequent dosing, bitter taste, and odor drugs are inappropriate for

ODTs (Bandari et al., 2008; Bharawaj et al., 2010; Saroha et al, 2010; Badgujar and Mundada, 2011).

1.1.2 Challenges in Formulating ODTs

Palatability: Most of drugs are bitter or have an undesired taste and odor that becomes critical to patient compliance. This is due to the issue that taste masking of bitter active ingredients is a major challenge especially for ODTs in the pharmaceutical industry.

Amount of drug: Some techniques are limited by the amount of drug that can be integrated into each unit dose. For example, the lyophilization technique requires dose to be lower than 400mg for in-soluble drugs and 60mg for soluble except for antibiotics, which are a relatively large dose (Seager1998; Ghosh et al., 2005).

Diameter of tablets: The size of the tablet plays a role on the effect of medication compliance. Larger tablets tend to be more difficult to swallow than smaller tablets. According to research, tablets that measure 7-8 mm are accepted as the easiest to swallow while anything larger than 8 mm causes difficulty. Thus, a size of that nature for a tablet causes challenges for pharmaceutical industries because it is difficult to achieve.

Hygroscopicity: Many ODTs are hygroscopic and cannot physically withstand normal conditions of temperature and humidity Therefore, protection is needed from humidity and that requires special packaging which ultimately increases production cost (Habib et al., 2000).

Mechanical strength: In order to facilitate ODTs to disintegrate in the oral cavity, they are made of either very porous or low compression force which creates friable and brittle tablets. This requires the need for cautious handling throughout the manufacturing process requiring specialized peel-off blister packing which can further add to the cost. Only few technologies can produce tablets that have sufficient hardness and robust to allow them to be packaged in multi-dose bottles, such as Wowtab® and Durasolv® (Chang et al., 2000; Hamilton and Luts, 2005).

Solubility: Hydrophilic active ingredients facilitate rapid disintegration of ODTs, but perhaps form eutectic mixtures. On the other hand, hydrophobic active ingredient retards disintegration of ODTs. This problem can be solved by using low hydrophobic active ingredients and low dose drugs. When the (Fu et al., 2004; Hirani et al., 2009).

1.1.3 Desired Criteria for ODTs

There are some preferable criteria to improve ODTs. Some of the criteria needed for improvement of ODTs are:

1. Disintegrate more quickly without leaving residue in mouth
2. Compatible bitter tasting drugs with taste masking technologies
3. Low sensitivity to environment condition such as humidity and temperature
4. Higher drug loading
5. Sufficient mechanical strength to withstand rigorous manufacturing process and storage conditions.

1.2 Disintegrating Agents

A disintegrant is an excipient added to tablet and capsule formulations to enhance and ensure a rapid break down into their primary particles (Figure1.1). In addition, it play as major role in improving the drug activity and bioavailability by breaking down the tablet to increase the available surface area and enhance a more rapid release of the drug substance. Disintegrating agents can be categorized depending on their organ: Natural or synthetic.

a) Natural: They are economically low in cost and readily available (e.g. Lepidus sativum, Locust bean gum, Xanthan gum, Soy polysaccharide, Chitosan gum Arabic, etc).
b) Synthetic: They are used at low concentration level and have a lesser impact on compressibility and flowability as shown in (Table1.1).

Table 1.1: Synthetic Disintegrating Agents.

Synthetic Disintegrating Agents	**Mechanism of Action**
Sodium starch glycolate (Explotab, Vivastar)	Swelling
Croscarmellose sodium (AC-Di-Sol, Primellose)	Swelling
Cross-linked polyvinylpyrrolidone (Crospovidone)	Swelling and wicking
Micro crystalline cellulose, MCC (Avicel 102)	Wicking
Low-substituted hydroxypropyl cellulose (L-HPC)	Swelling
Partially pregelatinized starch (PPG Starch)	Swelling
Cross-linked alginic acid (Alginic Acid NF)	Swelling and wicking
Calcium silicate	Wicking
Ion exchange resins (Indion 414, Tulsion 339)	Swelling

1.2.1 Mechanism of Tablet Disintegration

Disintegration is achieved through three main mechanisms: Wicking, swelling, and deformation. The swelling mechanism is the most common since almost all disintegrates swell to some extent (Zhao and Augsburger, 2005). The properties of material play important role in mechanism of disintegration (elastic, plastic and brittle) also type of disintegrating (super-disintegrating and disintegrating), type of polymer of disintegrating agents (Linear, Branched 2 dimensional and cross linked 3 dimensional) as shown in (Figure 1.2), and particle size of super-disintegrating agents effect on efficiency of disintegration (Zhao and Augsburger, 2006).

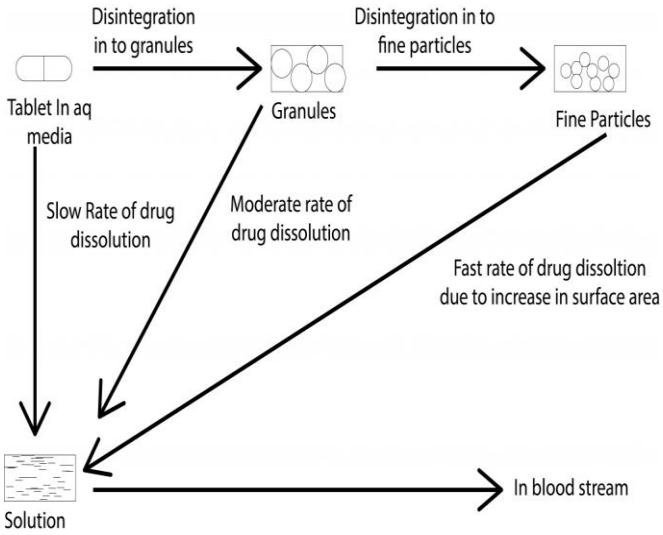

Figure 1.1: Tablets Disintegration.

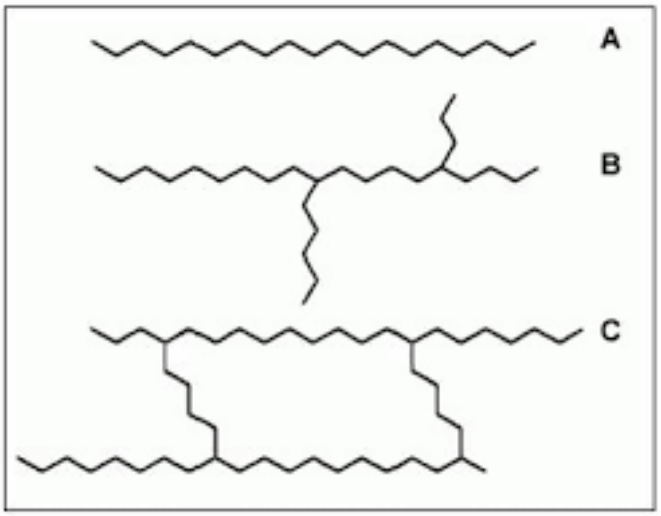

Figure 1.2: Type of Polymer.

1.2.1.1 Porosity and Capillary Action (Wicking)

Tablet porosity provides pathway for the penetration of fluid into tablets. Through porosities and capillaries, fluid enters into the tablet and breaks the tablet up by rupturing the intermolecular bond (Figure 1.3). Water is absorbed through tablet depends on type of drug and excipient (hydrophilicity) and parameter of compression force impacts this mechanism

through number and size of porosity. The ability of imbibitions into porous tablet to absorb water can be calculated by Washburn's equation:

$$L^2 = (\frac{\gamma Cos\theta}{2\eta}) \times rt \quad (1.1)$$

1.2.1.2 Swelling

Swelling is the most used mechanism of action for tablet disintegration. It has hydrophilic material cross-linked polymers, which swell from (10 to 1,000) times their own weight when placed in an aqueous environment as shown in (Figure 1.4). The Swelling of particles create pressure and stress within structure of tablet causing a breakage in the bonding. In reality, mild explosion occurs in stressed area to break all structure apart (Omidian and Park, 2008). Swelling agents should have a good water absorbing property. If it does not have a good water absorbing quality, it could be enhanced by adding a wetting or wicking agent to accomplish a complete swelling action (Goel et al., 2010). This mechanism is impacted by structure and degree of cross-linking. At the same time, porosity of the compact effects on disintegrating rate. High porosity gives a poor disintegration rate due to lack of adequate swelling force, while low porosity compacts at high compression force to prevent liquid entry and prolong the disintegration time. Thus, tablets should be prepared at the optimal porosity to provide sufficient mechanical strength without affecting the disintegration time (Desai and Heng, 2016).

1.2.1.3 Deformation

Rheology of material plays role on disintegrating agents. Under certain pressure particle is deformed dominant or permanent form. Elastic material is deformed permanently under force to create intermolecular bond. When this bond ruptures, the particles return to original size and disintegrate as shown in (Figure 1.5). Elastic material behavior is more desirable in this mechanism (Late and Banga, 2009).

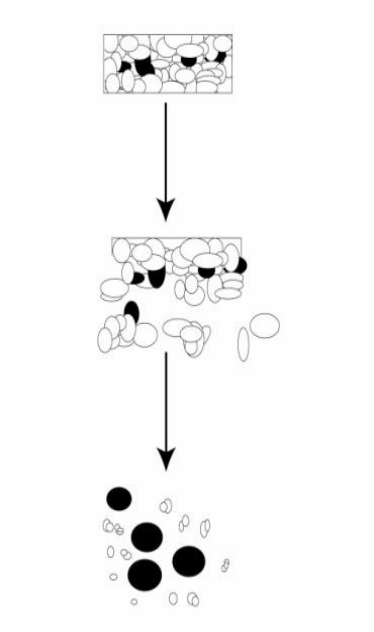

Figure 1.3: Swelling

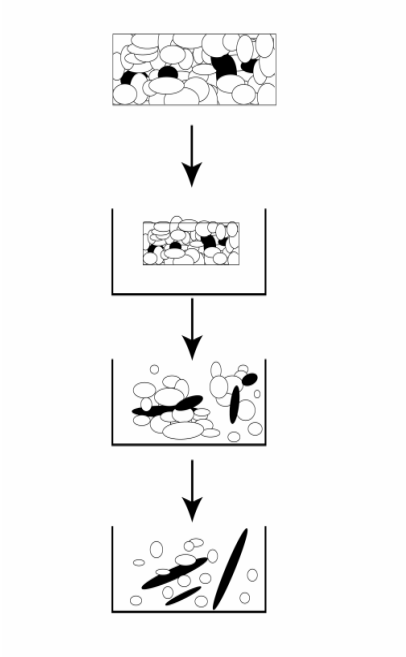

Figure 1.4: Wicking

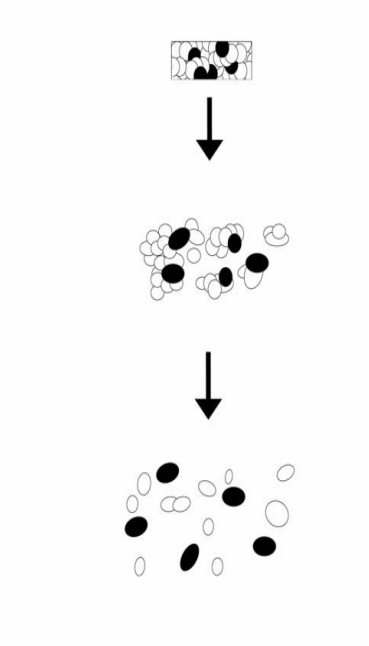

Figure 1.5: Deformation

1.2.2 Mode of Addition

The method of adding disintegrants can be incorporated at three stages: Intra-granular (pre-granulation), extra-granular (post-granulation), and/or distributed between intra and extra granular. Method of adding disintegration effects on time of disintegrating and tablets hardness (Shotton and Leonard, 1976).

a) Internal addition (intra-granular): In this method, disintegrating agent is blended with formulation powder at the granulation step. In the wet granulation process, adding intra-granular affect is achieved by wetting and drying in wet granulation process. This will influence the efficacy of disintegration.
b) External addition (extra-granular): In this method, disintegrating agent is blended with the prepared granules just before compression step. In wet granulation method extra-granular disintegrate faster than intra-granular because of the wetting and drying technique's ability to change hygroscopicity of disintegrates agents (Shotton and Leonard, 1976).

c) Internal and external addition: In this method, disintegration agent is added to formulation in two steps intra-granular and extra-granular disintegrants. Combination of intra-granular and extra-granular method increases efficacy of disintegrates, so this method can be more effective (Gordon et al., 1990).

1.3 Mannitol

Since ODTs are formulated to disintegrate in the oral cavity, they often cause an unpleasant taste and a rough sensation on the tongue during administration. This unpleasant sensation can markedly influence medication compliance. Conversely, taste palatability is important to formulate dosage form to achieve patient compliance and satisfaction especially for mouth dissolving or disintegrating tablets. Many active ingredients have an unpleasant taste or create unpleasant taste. Taste masking techniques are applied to mask or overcome the bitter or unpleasant taste of active ingredients. Bitterness of formulation limits the medication options available for physicians and patients leading to a decrease in therapeutic efficacy and compliance particularly in children and the elderly. The taste masking of bitter active ingredients is a major challenge especially for ODTs in the pharmaceutical industry (Douroumis, 2011). Due to these disadvantages, many techniques have been developed to improve ODTs acceptance by using a taste masking ingredient that does not prolong oral disintegration (Table 1.2). Techniques for masking unpleasant tastes are chiefly classified into three methods:

a) Physical methods are coating the drug itself or the drug containing granules.
b) Sensory methods that involve addition of substances such as sweetening agents, flavoring agents, etc.
c) Chemical methods that cause formation of organic acid salts and insoluble salts (Nakano et al., 2013).

Tablet 1.2: Taste Masking Techniques.

Techniques
Addition of flavoring and sweetening agents.
Microencapsulation and microspheres.
Ion exchange resins.
Inclusion complexes.
Granulation.
Adsorption.
Pro-drug approach.
Multiple emulsions.
Solid dispersion.
Molecular complexes.
Gel formation.
Mass extrusion method.
Use of salt and derivative.
Use of amino acids and protein hydrates.
Bitterness inhibitors.
Use of liposomes.

Mannitol is sugar alcohol which is water soluble, non-hygroscopic, and can appear in four different polymorphic forms. It exists in many physical forms including three anhydrous polymorphs (α, β and δ), mannitol hemihydrate and amorphous can be retained in the amorphous state if the other formulation components inhibit mannitol crystallization (Liao et al., 2007). Additionally, polymorphic is conversion by heating, friction, grinding, and tabletting (Yu et al., 1998; Juppo, 1996). The main disadvantage of the frequently used polymorph of mannitol in tablet formulations is its low compactability. Mannitol undergoes fragmentation under pressure leading to the formation of weak compacts (Yu et at., 1999). The pharmacopoeias are only referring to D-mannitol and it is one of the most commonly used

excipients in the ODTs as sweetening agents because high physiological tolerability, low toxicological concerns, chemical inertness (towards other excipients and the API), Good taste and mouth feel, High compactibility and flowability (required for DC), low prices and produces robust tablets and which allow for a directly compressible preparation with excellent mechanical properties, rapid dissolution, and good mouth feel (Ohrem et al., 2014). Concentration of Mannitol influence physiochemical, mechanical and Mannitol lyophilized. Decreasing Mannitol concentrations improves dissolution time. The advantage of mannitol is that it does not increase blood glucose content during metabolism which makes it safe to use in the diabetic population (Debord et al., 1987). Mechanically, at the same time, it has strong friction with die wall that may cause a problem during compaction and ejection (Yoshinari et al., 2001).

Mannitol powders: The choice of excipient for pharmaceutical applications in form of granulation and freeze drying because of ease of drying, porous structure, and preventing crystallinity structure from collapse, and characterized as plastic deformation (Roberts and Rowe, 1987).

Mannitol granular: An excellent diluent and binder for direct compression applications. Mannitol granular powders offer all the required properties of DC excipients because of free flowing and good compactibility with low friability, non-sensitivity to tabletting speed (allowing high productivity), lubricant non-sensitivity, good dilution potential, particle size and shape (spherical or rod, smooth or rough, large or small). It can be found commercial mannitol (without binder) and mannitol (with binder). Commercial mannitol has a very low a compressibility and a high friability (Serpelloni and Lemay, 1992). Also, spray-dried Mannitol can be impacted by different parameters during the spray drying process. Parameters such as feed concentration (w/w), outlet temperature (influence Mannitol particles surface: rough, smooth), feed rate (L/h), and rotation speed (rpm). These parameters extensively affect the flowability, compaction, and dissolution time (Littringer et al., 2012).

Freeze drying is the most commonly used excipients in pharmaceutical products because of its tendency to crystallize from frozen aqueous solutions and the high melting temperature (Kim

et al., 1998). Freezing rate and Mannitol concentration influence the crystal form of mannitol and prevent collapse crystallinity structure freeze drying. Furthermore, freeze drying generally exhibit rapid disintegration and dissolution due to their highly porous nature, which allows penetration of aqueous into the structure, resulting in disintegration. This process involves the transition of water from liquid to solid during freezing, and then solid to vapor during sublimation. In practical, the advantage of freeze drying is that the solution is frozen such that the final dry product is a network of solid occupying the same volume as the original solution. Resulting in a light and porous product, which is readily soluble. Mannitol is responsible for forming the highly porous matrix structure of the dosage form, and also providing crystallinity, hardness and elegance. Water is used as a manufacturing process media, which induces the porous structure upon sublimation during the freeze drying stage (Sastry et al., 2000).

1.4 Techniques of Preparing ODTs

Commercially available ODTs are prepared by various techniques. Conventional methods used in preparation of orally disintegrating tablets include freeze drying, tablet molding, spray drying, mass extrusion, cotton candy process, nanonization, sublimation, and direct compression. A major challenge in the development of orally disintegrating tablets is to achieve a good balance between tablet hardness, disintegration time, and taste. Compression pressure is important parameter in ODTs processes because low compression pressure produce dosage form has fast disintegrating time and low physical resistance due to be unsuitable for packaging in conventional blisters or bottles. The lyophilization and molding techniques produce an ODT that disintegrate within 30 seconds, but the result in both high friability and low physical resistance. On the other hand, direct compression ODTs has different characters such as less friability and longer disintegration time (Dobetti, 2001).

Technologies Used for Manufacturing of Orally Disintegrating Tablets:

Many technologies and various processes have been developed for preparing ODTs including conventional technologies and Non-Conventional Technologies (Velmurugan and Vinushitha, 2010).

1.4.1 Conventional Technologies

1.4.1.1 Freeze Drying/ Lyophilization

Lyophilization uses solvents that sublimed from the product after it becomes frozen. It creates an amorphous porous structure that can disintegrate rapidly. The major advantage of the freeze drying technique is that its use for temperature sensitive material also, those tablets are produced with a very fast disintegration rate and more palatable. However, this technique is expensive, time consuming, and high porosity in tablet structure produces weak mechanical strength. Consequently, requiring special packaging (Amborn el at.2001) such as PVC or PVDC plastic packs, may be packed into Aclar Laminates or Aluminum foil–foil preparations to protect the product from external moisture (Sastry et al., 2000), and its Fragility makes conventional packaging inappropriate for these products and has poor stability under stressed condition (Bikshapathi et al., 2011).

1.4.1.2 Spray Drying

Spray drying is largely used in pharmaceuticals because it produces highly porous tablets, fine powders, short disintegrating time (within 20 seconds) and rapid evaporation of solvents. Using a bulking agent (mannitol) in this technique increases the dissolution rate and Improves taste and adds effervescent optionally in minimal amount to accelerate the dissolution rate. Micro-encapsulated or nano-encapsulated can be used for active ingredients as taste masking (Fu et al., 2004).

1.4.1.3 Melt Granulation

In this process powders are effectively agglomerated by the use of binder (e.g. PEG-6-stearate) hydrophilic waxy binder that increase the physical strength of tablets and has low melting point. This can be liquefied or melted during the operations by utilizing high shear mixers which raises the temperature above the melting point of the binder through a heating jacket or by the heat of friction that produces by impeller blades (Pahwa et al., 2010; Perissutti et al., 2003).

1.4.1.4 Direct Compression

Direct Compression (DC) is the technique where tablets are compacted directly from mixtures of the drug and excipients. The tablet has fast disintegrating time and appropriate hardness and friability (Bi et al., 1999). This technique is a preferable because conventional equipment, few numbers of processes (compared to other techniques) and cost effective (Velmurugan and Vinushitha, 2010). Types of super-disintegrants, optimum concentrations and compression force can enhance disintegration properties because they are the most critical parameters of DC (Pabari and Ramtoola, 2012; Mizumoto et al., 2005).

1.4.1.5 The Cotton Candy Process

The Cotton Candy technique uses exceptional spinning mechanism to produce a floss like crystalline structure, as same as cotton candy. Fuisz Technologies has introduced the Shearform® technology to make Flash dose. In this process, the active ingredients are undergoing to centrifugal force and to a temperature gradient simultaneously. The speed of spinning is about 3,000–4,000 rpm, and the temperature gradient is about 180–250°C. This technique is limited because of its high temperature of gradient. Two systems are used to create the Shearform® technology.

a) Single floss this system made of (sucrose, sorbitol, and xylitol) produce efficient self binding property.
b) Dual floss uses two separate flosses. One is (xylitol) containing binder flosses and the other is flosses that have different sugar alcohols or saccharid. The floss is appropriate for the conventional tableting process because its flowability is improved. A hygroscopic material has to be used in the system to provide good self binding the final matrices (xylitol). It can be milled and blended with active ingredients and subsequently compressed into ODT (Acosta et al,. 1998; Fu et al., 2004).

1.4.1.6 Molding

This technique is prepared by using water soluble ingredients mostly sugars. Low moldable sugar is coated with high moldable sugar followed by a specific humidity treatment that allows

the blend mixture to pass through a very fine screen then moistened with a hydro-alcoholic solvent. Process ends by the evaporation of the solvent through air drying (Mizumoto et al., 1996; Shukla et al., 2009; Pahwa et al., 2010). Molded tablets have good taste because the dispersion matrix is made from water soluble sugars. Related to this process, compression pressure is lower than conventional tablets to create a porous in structure of tablets for accelerating disintegrating and improve the dissolution rate. The limitation of molded tablets is the mechanical strength and friability that occurs during packaging and transportation (Velmurugan and Vinushitha, 2010).

1.4.1.7 Sublimation

In this process, the inert volatile substances utilized are (Urea, Camphor etc). They are blended with active substances and excipients and then compacted into a tablet. Hence, the volatile substances are removed by sublimation leading to the creation of a porous structure. These compacted tablets which have high porosity (approximately 30%) are quickly dissolved within 15 seconds in saliva (Koizumi et al., 1997).

1.4.1.8 Mass Extrusion

This process depends on softening the active blend by using a solvent mixture of water soluble Polyethylene Glycol and Methanol. Next, expulsion of softened mass is put through the extruder or syringe to get a cylindrical shaped. Afterwards, the heated blade is used to cut the cylindrical shaped masses into small parts. To mask the taste, this process can also be used to coat granules of bitter drugs (Gryczke et al., 2011; Velmurugan and Vinushitha, 2010).

1.4.1.9 Nanonization

Nanonization is the process of diminishing the particle size of Active Pharmaceutical Ingredients (APIs) and excipients by utilizing the wet milling operations. In detail, this system is convenient for poorly water-soluble drugs (Sahu et al., 2012) because it reduces the particle size and increases the particle surface area. Therefore, nano-particles lead to better dissolution and fast disintegration. The benefits of this technique are low cost-effective manufacturing process and conventional packaging.

1.4.2 Non-Conventional Technologies

Several technologies have been developed on the basis of formulation aspects and different processes. Resulting dosage forms vary on several parameters like mechanical strength, porosity, stability, taste, dissolution rate, and disintegrating time. (Table 1.3) shows the list of unique patented technologies Lyophilization (Zydis®, Quicksolv®, Lyoc®, Nanocrystal Technology®, and Nanomelt®). Direct compression (Flashtab®, Orasolv®, Durasolv®, Wowtab®, Ziplets®, Frosta®, Pharmaburst Technology®, and Dispersible Tablet Technology®). Cotton candy process (FlashDose® and Sheaform Technology®) OraQuick® Ceform Technology® Advatab®

Table 1.3: Non-Conventional Technologies.

Name of Company	Patented Technology	Used Technique	Advantage(s)
R. P. Scherer Corporation	Zydis	Lyophilization	Highly porous in nature, quick dissolution, and increased bioavailability
Cima Labs, Inc.	Orasolv	Direct Compression	Unique taste masking, fast dissolution, and require conventional
Cima Labs, Inc	Durasolv	Molding	Good rigidity
Yamanouchi Pharma Technologies, Inc.	Wow Tab	Compression Molded Tablets	Adequate dissolution rate and hardness
Ethypharm	Flash Tab	Effervescent disintegrants microencapsulated drug compression	Conventional tableting technology required
Eurand Pharmaceutical Inc	Advatab	Microcaps and diffuscap CR Technology	High drug loading and improved mechanical strength
Janssen Pharmaceuticals	Quicksolv	Lyophilization	Short disintegration time and good mouth feel
KV Pharmaceutical Co., Inc.	Oraquick	Micromask Taste Masking	Significant friability and appropriate for thermolabile drugs
Eurand International	Ziplets	Molding	Sufficient mechanical strength
Fuisz Technology, Ltd.	Flashdose	Cotton Candy Process	Highly porous in nature and pleasant mouth feel
Farmalyoc	Lyoc	Lyophilization	Accommodate high dose and disintegrates rapidly

CHAPTER TWO

LITERATURE REVIEW

2.1 Literature Review:

Howden (2004) has evaluated dysphagia affects a large and increasing number of individuals in the United States, particularly the elderly and those who are neurologically impaired. Swallowing difficulties maybe due to age-related changes in Oropharyngeal and oesophageal functioning as well as Central Nervous System (CNS) diseases such as stroke, Parkinson disease and psychiatric patients. Dysphagia is associated with increased morbidity and mortality. An evaluation of the physiology of swallowing and the pathophysiology of dysphagia is essential for appropriate patient management. Careful history, physical examination, and estimation of radiologic and endoscopic studies should differentiate oropharyngeal and oesophageal etiologies of dysphagia and differentiate mechanical disorders from functional disorders.

Carnaby et al., (2005) have estimated dysphagia is a common result of many health problems affecting more than 18 million adults in United States and will possibly to increase in the future. A recent national survey exposed that over (40%) of adults in the general community experience problems with swallowing pills. These issues were caused patients to delay taking medications and sometimes omitted their dose completely. In this study, ODTs formulation provided a technique of delivery that did not require swallowing and was the preferred choice for dysphagic patients and have shown to provide benefits to adults with dysphagia such as suitability, compliance, and accuracy of dosing.

Popa and Gafiţanu, (2003) have said that the pharmaceutical market recently shows an increasing interest in ODTs due to their good suitability among certain age categories including the elderly, children, and other patients. Some of the methods of manufacturing such

tablets have expanded industrial applicability: Molding, lyophilization and direct compression with highly soluble excipients, super-disintegrates and/or effervescent systems. Some of the patients have had a good impact on the pharmaceutical market according to their acceptance and satisfaction. More improvements are predictable in the next few years, with new drugs to be formulated in this field as fast disintegrating tablets formulations.

Fuet al., (2004) have noted in this review various formulations and technologies developed to accomplish fast disintegration of tablets in the oral cavity. This review discusses in detail ODT technologies according to lyophilization, molding, sublimation, and compaction, as well as approaches to improving the ODT properties. For example, spray drying, moisture treatment, sintering, and usage of sugar-based disintegrate. In addition, taste masking technologies, experimental measurements of disintegration times and clinical studies had also discussed.

Gordon et al., (1990) have tested and evaluated physical resistance and time of disintegration for poorly soluble drugs when incorporated with super-disintegrating agents (intra-granular, extra-granular and intra-extra-granular). Crossmellose sodium was used as a super-disintegrating and the results confirmed that tablet friability was not affected by the incorporating method of super disintegration. This study indicated that incorporating disintegrating extra-granular will break up tablet to primary granules and will not disintegrate further, while incorporating disintegrating intra-granular will cause tablet to disintegrate into primary particles. In addition to that, tablet friability will not be influenced by the method of incorporation.

Gordon et al., (1993) have investigated the effectiveness of the mode of super-disintegrants incorporation in wet granulated tablets. Three super-disintegrants were used (sodium starch glycolate, crospovidone, and croscarmellose sodium), then incorporated with three modes of addition extra-granular, intra-granularly and equally between the two phases, then dried formulation with three different level of moisture content. The result showed that extra-granular was a faster dissolution than equally incorporated and both of them (intra-granularly

and equally between the two phases) faster than intra-granularly. The super-disintegrants were faster dissolution in natural pH medium than in acidic. Granulation moisture content was found to have an impact on tablet dissolution.

Kuno et al., (2008) have evaluated the effect of lubricants on the characteristics of orally disintegrating tablets manufactured using the phase transition of sugar alcohol. By directly compressing a mixture containing lactose–xylitol the tablets were produced. The effect of the type of lubricant on the tablet characteristics was evaluated by using Magnesium Stearate (Mg-S), Sodium Stearyl Fumarate (SSF) and talc as lubricants. The result revealed that the hardness and time of disintegration are increased in the tablets that contained Magnesium Stearate and Sodium Stearyl Fumarate. In contrast, the oral disintegration time of the tablets containing talc was not changed despite of an increase in hardness. The water absorption rate of the tablets containing talc was much faster than other lubricants, also heating increased water absorption in tablet containing talc. Thus, talc was demonstrated to be the most desirable lubricant for the preparation of ODTs based on the principle of the phase transition of sugar alcohol.

Koizumi et al., (1997) used sublimation for preparing a tablet which is rapidly disintegrates by DC. Mannitol was used for its water solubility characteristic and sweetness, camphor as the sublimating material, and meclizine (antidinic agent) as an active ingredient. The tablets were prepared with different percentages between mannitol and camphor by dissolving mannitol and camphor in a water media followed by the sublimation process of camphor. The results showed a high ratio of camphor to mannitol due to insufficient strength in final product. This is because number porosities in tablet structure will be increased after camphor sublimation and decrease disintegrating time. After meclizine was added, tablet hardness increased while disintegrating time remained the same when compared to tablets without meclizine.

Mohapatra et al., (2014) in this study have prepared tablets of metformin by using microcrystalline cellulose in direct compression. Nonetheless, the tablets showed erosion

behavior rather than disintegration. Lactose incorporating created pores causing burst release of drug. However, these tablets affected the palpability. Incorporating lactose still gave a bitter taste because increased amount of lactose showed poor compressibility (capping) and increased disintegrating time. Finally, spray-dried mannitol was used to prepare tablets by wet granulation (10% polyvinylpyrrolidone in Isopropyl alcohol as binder). This resulted in a desired mouth feel and fast disintegration time.

Serpelloni and Lemay, (1992) have invented a method of preparing directly compressible granular mannitol by an extrusion treatment inside an installation comprising of a heating zone and an extrusion die. Mannitol that was prepared by this technique had an intermediate friability between that of commercial mannitol (without binder) and mannitol (with binder) and shows very close compressibility to that of mannitol with a binder and extremely greater than that of commercial mannitol.

Liao et al., (2007) have studied the effect of processing conditions of the lyophilization cycle of a protein formulation on the physical state of mannitol during various stages. Mannitol did not crystallize even when the solution for lyophilization was cooled at a cooling rate of 1-C/min. In the absence of the protein, a mixture of D-mannitol and mannitol hemihydrate was obtained at both low and high annealing temperatures nevertheless, in the presence of protein; the fast cooling rate promoted D-mannitol crystallization and inhibited formation of mannitol hemihydrate. However, the slow cooling rate facilitated the formation of mannitol hemihydrate which is unstable under ambient conditions and requires another exposure high drying temperature to convert it to anhydrous form. The study concluded that lyophilization conditions influenced the physical form of the final lyophilized mannitol and the presence of protein promotes formation of D-mannitol and inhibits formation of mannitol hemihydrate.

Schneid et al., (2008) have studied the impaction of multi-component when incorporated with freeze drying mannitol. Despite mannitol being popular as a crystalline bulking agent in freeze drying, it tends to form different crystalline alteration which may cause negative impact on

stability during storage period. Sucrose, trehalose and citric acid were used as additives on mannitol. There was an analysis on residual-moisture, x-ray powder diffraction, and differential scanning calorimetry. The findings suggested that any small amount of additive causes significant changes in crystalline of mannitol and residual moisture.

Littringer et al., (2012) have investigated the influence of spray drying process parameters related to product properties. Surface topography, size, breaking strength, and polymorphism of mannitol, were all investigated through four parameters: Feed concentration (10 and 20% [w/w]), gas heater temperature (170 and 190C), feed rate (10 and 20 L/h), and atomizer rotation speed (6,300 and 8,100 rpm). Particle size was influenced by the rotation speed and feed concentration. Higher rotation speeds and lower feed concentrations resulted in smaller particles. The strength of the dried particles was significantly influenced by gas heater temperature and feed rate. The higher the gas heater temperatures and high feed rates, the lower the strength of the particles became. Moreover, the process parameters had no affect on the polymorphism. The aim of this study was to prepare carrier particles for dry powder inhalers of sufficient size and variable surface roughness. This revealed that drying air outlet temperature is the main parameter for variations in surface properties of spray-dried mannitol. Lower temperatures resulted in the formation of large rod-shaped single crystals and rough surfaces while higher temperatures caused smoother surfaces.

Xu et al., (2008) have evaluated the potential of microspheres for taste masking in ODTs by using spray drying process to formulate microspheres. After that, the microspheres were incorporated with other excipients to form ODTs. The process parameters were solid concentration and feed rate. The study evaluated six volunteers who confirmed that the tablets disintegrated within 30 seconds and taste masking microspheres enhanced the taste significantly. In contrast, the microspheres decreased the bioavailability and inhibited the release of famotidine (active ingredients) significantly. The study concluded that microspheres were produced by spray-dried can effectively mask the bitter taste and can be incorporated in ODTs. Another finding showed the microspheres particles were affected by both solid concentration and feed rate.

Shu et al., (2002) have used direct compression to develop rapidly disintegrating tablets by using rod mill to obtain co-ground mixture from D-mannitol and crospovidone. After that non-ground mixture was mixed with (mannitol, crospovidone, and Mg-St). Crospovidone was used as a co-grinding agent for mannitol. The findings suggested that adding co-ground mixture of D-mannitol and crospovidone is useful in enhancing hardness of the tablets that could not be achieved by addition of their individual ground mixture. Crospovidone is useful in improving hardness of the tablets that could not be achieved by addition of their individually ground mixture through increasing the contact area among powder particles. The characteristic of tablets hardness and the time of disintegration were measured. The particle diameter and specific surface area of the co-ground mixture were also measured. The tablets manufactured from a physical mixture of 30% (w/w) co-ground mixture of D-mannitol and crospovidone (mixed ratio 9: 1) with 65.5% (w/w) of non-ground mannitol, 4% (w/w) of crospovidone, and 0.5% (w/w) of magnesium stearate had good properties for rapidly disintegrating tablets in the oral cavity. They showed the hardness of 4.9 kg and disintegration time of 33seconds. Grinding increases surface area of D-mannitol particle and this method was applicable as a remedy for solubility issues and adding crospovidone as a grinding property helped increase hardness of tablets.

Goel et al., (2009) have examined improving mechanical strength of ODTs of ondansetron HCl by wet granulation or direct compression method. Combination of glycine and chitosan was used as a sweet tasting and disintegrating system. They have observed influencing of ionized and unionized state for chitosan and glycine on the disintegration of ODTs. The ionization resulted from wet granulation method, reduced the wicking efficiency of glycine and decreased the swelling property of chitosan by increasing of disintegration time (DT), wetting time (WT) and water absorption ratio (WAR). Chitosan was presented in unionized state and decreased the disintegration time (DT) when the concentration of chitosan increased. The ODTs formulated with a mixture of (chitosan and glycine) showed higher mechanical strength and lower disintegrating time compared with ODTs containing super-disintegrants.

Brniaket al., (2015) have evaluated of methods used to determine the disintegration time of ODTs and correlated them with in-vivo results. In practical, six groups of ODTs were prepared by direct compression. The study measured their mechanical properties and disintegration times with pharmacopoeia and alternative methods, and later compared with vivo result. Disintegration tests showed great variability in the data measured with different methods. The shortest disintegration time was 2.3 seconds while the longest exceeded 3 minutes, the results between in-vitro and in-vivo recorded with big differences. This study confirmed pharmacopoeial methods that used for measuring disintegration time of ODTs cannot be effective for predicting time of disintegrating in vivo because of variable parameters during the test such as volume of medium, temperature, and the type of forces acting on the tablet in vivo (tongue pressure and movement).

Chaudhari et al. (2014) have prepared formulation to mask the bitter taste of Doxazosin Mesylate by formulating ODTs of taste masked drug that include spray drying technique and Eudragit powdered E-100 as a polymer for microspheres coating. Eudragit was used because it dissolves at a pH of less than five while the pH of the buccal cavity ranges from 5.8-7.4. Microspheres are prepared in different ratio drug: Polymer 1:1, 1:2, 1:3, 1:4, and 1:5. The tablets formulated were mixed with different types and concentration of super disintegrants and granulated mannitol as (a diluent) and compressed by the direct compression method. The formulations were evaluated by their hardness, friability, vivo disintegrating time, and vitro drug release. In conclusion, the spray drying of the drug with the polymer-Eudragit® has not affected its release.

Chandrasekhar et al., (2009) have investigated to optimize ODTs by freeze drying to obtain sufficient mechanical strength to withstand physical handling, also have a rapid disintegration time, and improved viscosity upon the addition of bio-adhesive polymers. This research divided into three stages, stage 1 added gelatin binder in different concentration 2% and 5% and evaluated hardness and disintegrating time. Stage 2 added the saccharides (sorbitol, mannitol, and sucrose) between 10% and 80%. Stage 3 added viscosity-modifying polymer (carbopol) in concentration between 2% and 10% to improve retention (bio-adhesion) of a

disintegrating tablet in an oral cavity. They have concluded increase ratio of gelatin will increase hardness and effect on disintegrating time. On the other hand, addition of mannitol in concentration 50% formulation had the best hardness and shortest disintegrating time.

Nakanoet al., (2013) designed ODTs of pioglitazone and evaluated the taste by using a visual analog scale (VAS) analysis. Two methods were used for taste masking: physical and sensory. The results indicated that physical masking could suppress the bitterness, but not the astringent. The sensory method suppressed both the bitterness and astringent, and offered a slight sweetness. In general, palatability of the orally disintegrating tablets was considered enhanced. In conclusion, visual analog scale was a useful tool to evaluate the taste of orally disintegrating tablets and sensory masking.

Kim et al., (1998) have studied the physical state of freeze-dried mannitol when mannitol is present as a single component under two variable parameters: Freezing rate and mannitol concentration. The glass transition temperature of amorphous mannitol were measured then were able to determine the relative concentration threshold above which crystalline mannitol can be observed by x-ray powder diffraction. They found that both freezing rate and mannitol concentration influence the crystal form of mannitol in the freeze-dried solid. The results slow freezing of 10% mannitol creates a mixture of the (δ and β) polymorphs, while fast freezing of the same solution creates the δ form. Fast freezing of 5% mannitol produces the β form. The threshold concentration above which crystalline mannitol is detected in the freeze-dried solid by X-ray diffraction is about 30% (w/w) regardless mannitol is present as a single component or two-component.and nature of the second component. The glass transition glass transition decreases markedly as the relative concentration of mannitol increases. This study recommended the need for a more and better understanding of the physical chemistry properties of freeze drying of mannitol containing formulations in order to predict and avoid unpleasant effects of mannitol on physical and chemical stability of the freeze-dried solid.

Mizumoto et al., (1996) have invented a molding technique which quickly disintegrates (within approximately 1-120 seconds) and has an adequate hardness (withstands the production steps and distribution stages). Low moldable a saccharide granulates with high moldable to prepare compressed moldings tables under compression force lower than conventional tablets.

Okuda et al., (2009) have designed new preparation method to produce rapid disintegration granules (RGD) for designing a new orally disintegrating tablet (ODT) that has high hardness and a fast oral disintegration rate. Spray coated saccharide, such as trehalose, mannitol, or lactose was used with suspension of corn starch using a fluidized bed granulator. The granules obtained had very large surface areas, narrow particle size distribution, and numerous micro-pores. This suspension method is simple and does not require applying special equipment.

Ahmed et al., (2006) have prepared a lyophilized tablet of ketoprofen by using freeze drying and developed orally disintegrating ketoprofen tablets. The solubility and dissolution rate of poorly water-soluble (ketoprofen) was improved by this technique.

CHAPTER THREE

MATERIALS AND METHODS

3.1 Material:

Lyophilized mannitol was produced in Near East University Laboratory. Ascorbic acid powder, Avicel, AC-DI-SOL, Sodium lauryl sulphate, Aerosil, and Polyethylene glycol 4000 were provided by Eastern Mediterranean University. Mannitol (Powder, Granular, spray-dried) was gifted by IMCD Company.

Table 3.1: Materials used in this study

Material	Lot#	Company
Ascorbic Acid	201306002	DOGA Ilaç
Mannogem Powder (mannitol, USP/EP)	121606837F	SPI Pharma
Mannogem EZ (spray-dried mannitol)	121707889	SPI Pharma
Mannogem Granular (Granular mannitol)	121808874	SPI Pharma
AC-DI-SOL SD-711 (croscarmellose sodium crosslinked)	TN11822881	IMCD
Sodium Lauryl Sulphate	151-21-3	emirkimya
Avicel PH 102 (microcrystalline cellulose)	71733C	FMC
Polyethylene Glycol 4000	25322-86-4	Merck Group
Silicon Dioxide	7631-86-9	ZAG kimya

3.2 Methods:

3.2.1 Preparation of materials by freeze drying

Freeze drying is the exclusive drying process for heat sensitive materials. In pharmaceutical industry, aqueous solution is water and it is usually removed by freeze drying, leaving the dried products to be packaged or further processed.

The freeze drying process normally involves three stages: Freezing, primary drying and secondary drying. Throughout the primary drying, water vapor is gradually removed from the frozen material by sublimation at low temperature. The pressure must be lower than the vapor pressure of ice in order for sublimation to take place. The secondary drying is started by increasing the temperature regularly to room temperature or above and reducing the chamber pressure to remove bound water (Desorption).

3.2.1.1 Freezing

Freezing is the first step of a freeze drying process (Liapis and Bruttini, 1995). The freeze-dried samples were prepared by following these steps. Each material was dissolved and stirred in a water bath (BUCHI) at 30 C° for 20 minutes, followed by freezing stage at -18°C.

3.2.1.2 Primary and Secondary Drying

Freeze drying experiments were carried out using an (Christ-ALPHA 1-4 LD PLUS) as shown in (Figure 3.1). After a solution was frozen, the next step in the freeze drying process is usually primary drying. Primary drying is typically carried out at very low pressures using vacuum pump. The primary drying (Ice Sublimation) was carried out until all the crystalline ice was removed. The sample was then heated to the secondary drying temperature (desorption) at room temperature 25 C° where the drying was continued for the desired time period (Franks, 1998).

3.2.2 Preparation of Lyophilized Samples

3.2.2.1 Mannitol

Mannitol was prepared by dissolving 100 g of mannitol in 500 ml of water until a clear solution was obtained. The solution was slowly cooled down to room temperature, and further cooled to -18 °C in the fridge, followed by Primary and Secondary Dry in gas as shown in (Figure 3.2).

3.2.2.2 Ascorbic Acid

Ascorbic acid solution was prepared by dissolving 100 g in 350 ml of water and was frozen at -18°C. The solution was slowly cooled down to room temperature, and further cooled to -18 °C in the fridge, followed by Primary and Secondary as shown in (Figure 3.3).

3.2.2.3 Mannitol and Ascorbic Acid

Mannitol 50 g and ascorbic solutions 50 g were prepared by dissolving them in 400 ml of water and were frozen to -18°C. The solution was slowly cooled down to room temperature, and further cooled to -18 °C in the fridge, followed by Primary and Secondary Drying.

Figure 3.1: Freeze Dryer (Christ-ALPHA 1-4 LD PLUS).

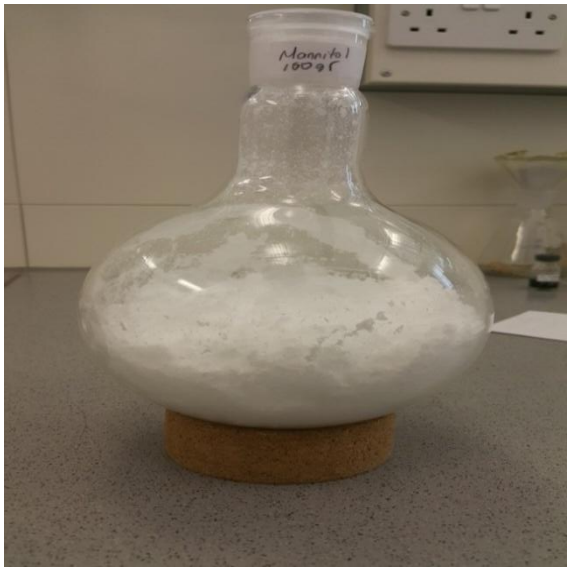

Figure 3.2: Lyophilized Mannitol.

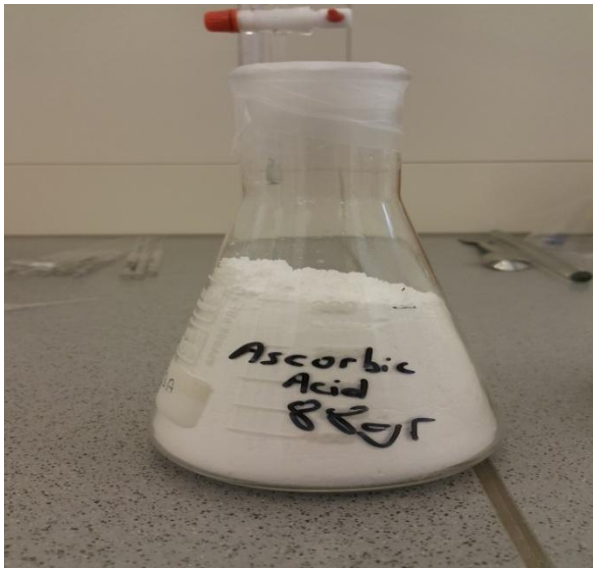

Figure 3.3: Lyophilized Ascorbic Acid.

3.3 Preparation of ODT by Direct compression

The 350 mg tablets of different ODT formulations were prepared by direct compression method. All the components of the formulation were first passed through (500 µm) mesh sieve separately in sieve shaker (AS 200, Retsch, Germany) as shown in (Figure 3.4). The ingredients of ODT were weighed individually and accurately by an analytical balance (Electrical balance, Mettler Toledo) as shown in (Figure 3.5). Ascorbic acid, PEG 4000, Avicel PH102, sodium lauryl sulphate, AC-DI-SOL, and mannitol (spray-dried, powder, granular, and lyophilized) were blended in Cube Mixer (KB, ERWEKA, GmbH, Germany) as shown in (Figure 3.6) for fifteen minutes and rotated at 200 rpm. Thereafter aerosil was added and mixed with the powder blend for a further five minutes. After mixing, the powder was transferred to be compressed by tablet a press (Single Punch Eccentric Tablet Press EP-1, ERWEKA, GmbH, Germany) as shown in (Figure 3.7). Different adjustments of the machine settings were tested. The adjustment which gave the highest possible hardness value with the shortest disintegration time was selected and applied to all tablet formulations. The powder mixture was compressed at ($40N \mp 5$) and the diameter was 10 mm for Mannitol (Powder, granular and spray-dried) then diameter 12mm for (lyophilized ascorbic acid, lyophilized mannitol and lyophilized ascorbic acid with spray-dried mannitol).

Table 3.2: Composition of ODT Containing Ascorbic Acid.

	F1	F2	F3	F4	F5	F6
Powder Mannitol	157.5mg	-----	-----	-----	-----	-----
Granular Mannitol	-----	157.5mg	-----	-----	-----	-----
Spray-dried Mannitol	-----	-----	157.5mg	-----	-----	157.5mg
Lyophilized Mannitol	-----	-----	-----	157.5mg	157.5mg	-----
Lyophilized Ascorbic acid	-----	-----	-----	-----	70 mg	70 mg
Avicel PH102	73.5 mg	73.5 mg	73.5 mg	73.5 mg	73.5 mg	73.5 mg
Ascorbic Acid	70 mg	70 mg	70 mg	70 mg	-----	-----
AC-DI-SOL	17.5 mg	17.5 mg	17.5 mg	17.5 mg	17.5 mg	17.5 mg
Sodium lauryl sulphate	14 mg	14 mg	14 mg	14 mg	14 mg	14 mg
Aerosil	10.5 mg	10.5 mg	10.5 mg	10.5 mg	10.5 mg	10.5 mg
Polyethylene glycol 4000	7 mg	7 mg	7 mg	7 mg	7 mg	7 mg
Total	350 mg	350 mg	350 mg	350 mg	350 mg	350 mg

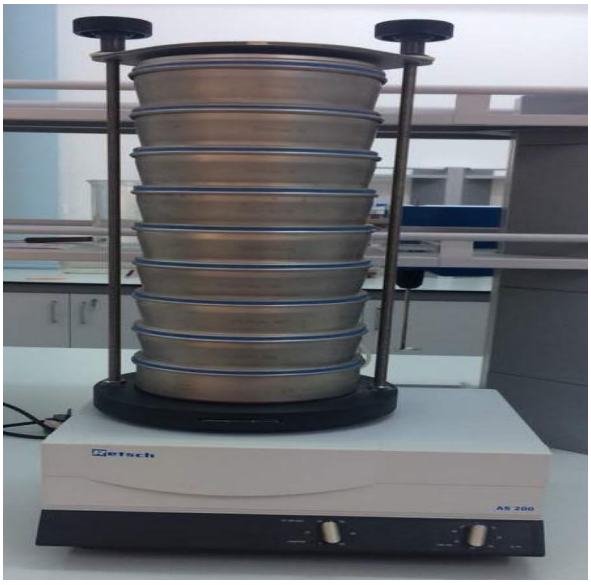

Figure 3.4: Sieve Shaker, AS 200.

Figure 3.5: Electrical Balance.

Figure 3.6: Cube Mixer KB.

Figure 3.7: Single Punch Tablet Press EP-1.

3.4 Physical Characterization

3.4.1 Flow Properties and Compressibility

Compressibility index (Carr's index) values, Hausner Ratio, and Flodex tool of the different formulations were determined by measuring the bulk volume then calculate volumes of the powders after subjecting to 200 taps in a graduated measuring cylinder by using the following equations:

$$\text{Carr's index} = \frac{V_B - V_T}{V_B} \times 100 \quad (3.1)$$

$$\text{Hausner Ratio} = \frac{V_T}{V_B} \quad (3.2)$$

V_B is bulk volume and V_T is tapped volume

3.4.2 Tablet Weight

20 tablets were selected randomly from the lot and weighted separately to check for weight variation. The test was achieved according to specifications given in the international

pharmacopeia (IP). The most acceptable limit is ± 5% deviation of an individual mass from average mass as shown in (Table 3.3).

Table 3.3: Weight Variation Specification as per IP.

Average Weight of Tablet	% Deviation
80 mg or less	± 10
More than 80 mg but less than 250 mg	± 7.5
250 mg or more	±5

3.4.3 Tablet Thickness

The thickness of tablet was measured by a hardness tester (Erweka TBH 125, GmbH, Germany) as shown in (Figure 3.8). Ten tablets were taken and measured their thickness by placing vertically into the testing chamber of the hardness tester.

3.4.4 Tablet Hardness

Tablet Hardness or tablet crushing strength for ten tablets were calculated by placing horizontally into the testing chamber of hardness tester (Erweka TBH 125, GmbH, Germany) at a speed of 20 mm/min. as shown in (Figure 3.8).

Figure 3.8: Tablet Thickness and Hardness Tester, TBH 125.

3.4.5 Tablet Friability

Friability is the loss of tablet weight in the container or package, due to removal of fine particles from the surface. This in process quality control test is achieved to make sure the ability of tablets to withstand during stage of processing, handling, transportation, and shipment. Tablet friability was evaluated using a tablet friability tester (Erweka TBH, GmbH, Germany) as shown in (Figure 3.9). Twenty tablets were positioned in the friabilator and rotated at 25 rpm for four minutes. Tablet dust was removed pre-testing and post-testing to remove excess powder to get accurate tablet mass. The weights of all tablets in the drum after 100 revolutions have measured. The test was made to find out the effects of friction and shock on tablet. Compressed tablets should not lose more than 1% of weight.

$$\text{Percentage Friability} = \frac{W_1 - W_2}{W_1} \times 100 \qquad (3.3)$$

According to B.P/I.P = Percentage friability should be not more than 0.8% - 1.0%
According to U.S.P = Percentage of friability should be not more than 4%.

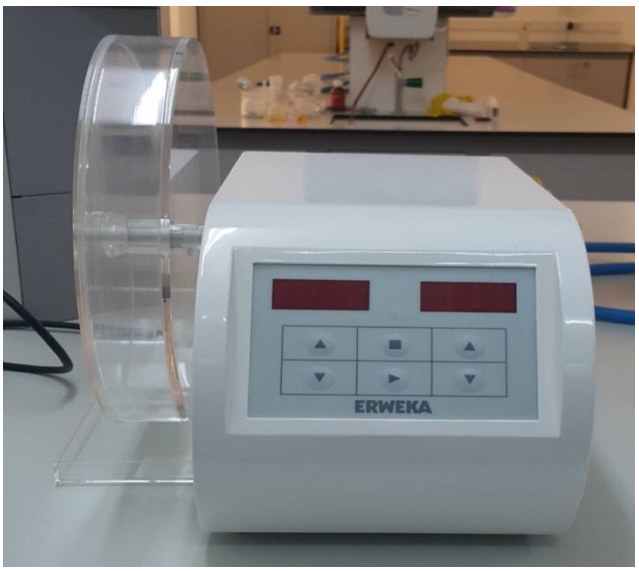

Figure 3.9: Tablet Friability Tester.

3.4.6 In-Vitro Disintegration Time

Tablet disintegration time was evaluated using a Disintegration Tester (ZT 320 ERWEKA, GmbH, Germany) as shown in (Figure 3.10). The disintegration time was measured in vitro using US pharmacopeia monograph ([701] disintegration) tablet put in a 1000 ml beaker containing 900 ml of distilled water which maintained at 37±0.1°C used as the disintegration medium and a paddle rotating at 100 rpm. Tablets were measured individually and the time recorded for each tablet, which disintegrated without leaving any residue in the basket (Harada et al., 2006).

3.4.7 Evaluation of Palatability

This evaluation was accomplished by five healthy volunteers. Each of the six formulations were transferred and labeled only with formulation code. One tablet of every formulation was given to volunteer for evaluation of palatability study (mouth feels and taste). Every volunteer at random took one tablet and placed it on the tongue during which the palatability taste at various times was determined. At the end, the mouth was washed with distilled water and then each volunteer took another tablet formulation. The time interval between evaluations in the same volunteer was 15 minutes. The taste was evaluated and allocate as numerical values, 0=tasteless, 1= non-acceptable, 2=bitter, 3=Acceptable, 4=Good, and 5=Excellent. Also, the mouth feeling was evaluated and allocate as numerical values 0=smoothness, 1= Grittiness, respectively as shown in (Table 3.4).

Figure 3.10: Disintegration Tester.

Table 3.4: Evaluation of Palatability Values.

Scale						
Effect	0	1	2	3	4	5
Taste	Tasteless	Non-acceptable	Bitter	Acceptable	Good	Excellent
Mouth feeling	Smoothness	Grittiness				

CHAPTER FOUR

RESULTS AND DISCUSSION

4.1 Results and Discussion:

In this study, an ODT formulation was developed by using lyophilized mannitol and did comparing with commercially available mannitol (granular, powder, and spray-dried) and ascorbic acid as an API. Mannitol was used as taste masking to improve palatability of ODT. The result is very important to determine the best formula to achieve ODTs with good taste, hardness, size, friability, and fast disintegration time.

Direct compression method was used because of it is easy manufacturing and lower cost (Medina and Kumar, 2006). Moreover, the tablet has fast disintegrating time and appropriate hardness and friability (Bi et al., 1999). The results are very favorable with respect disintegration time within limits, size of tablets, and palatability. Disadvantages such as it is not suitable for poor flowability powder and cause weight variations that impact on hardness and friability, also static charge during mixing and compaction stages may cause agglomeration in final blended powder. The formulation of ODTs mainly depends on the type, mechanism and mode of addition of super-disintegrants, which applied in formulation like Croscarmellose Sodium (Ac-Di-Sol SD-711). Super-disintegrants are generally used for developing ODTs or for improving disintegrating tablets to primary form (powder). They are used from 10 to 20 wt % in ODT formulations and it can be higher or lower in some cases. Thus, in developing an ODT formulation for direct compression, selecting the optimal super-disintegrant is critical (Camarco et al., 2006). Also compressibility characteristics of the super-disintegrants are important. ODT formulations are recommended to have low hardness to allow porosity within limit range to facilitate disintegrating of tablet but pores in tablet structure will decrease performance of disintegrating agents that work by swelling mechanisms. Croscarmellose Sodium were used because its mechanism in both swelling and wicking. Micro crystalline cellulose (Avicel PH-102) was used as direct compressible diluents and it has good compatibility at low compaction force because it’s plastic properties and it is not sensitive to lubrication in formula. In this study different of Mannitol grades were used as

shown in (Table 3.1) to improve palatability of ODT tablets, mannitol has properties that make it good choice for our studying non-hygroscopic, sweetness, cooling effects, crystal forming agents during lyophilization stages, prevents collapse system freeze drying, and doesn't interact with water. Mannitol metabolism does not cause high blood sugar. Different mannitol grades that we used in formulations, we faced challenges during our compaction process included in flowability, compressibility, and lubrication need.

Flow properties:

The flow properties of the ODT were analyzed by Bulk density (Figure 4.1), Tapped density (Figure 4.2), Carr's Index (Figure 4.3) Hausner Ratio (Figure 4.4) and Flodex equipment as shown in (Figure 4.1). Bulk density was found to be in the range of 0.27±0.02 to 0.45±0.02 g/ml. Tapped density was in the range of 0.35±0.01 and 0.55±0.15 g/ml. Carr's Index was between 17% and 30%. As shown in (Table 4.1). The preformulation study conducted on powder evaluation for flow property showed Carr's Index above 17. All the formulations exhibited passable and poor flowability properties. Hence mannitol spray-dried had good flowability and compressibility properties comparing to mannitol powder, granular, and lyophilized as shown in (Table 4.1).

Table 4.1: Flow Properties and Compressibility.

Powder mixture	Density (g/ml)		Flow properties		
	Bulk	Tapped	Carr's index (%)	Hausner ratio	Flodex equipment
F1	0.41	0.54	23.00	1.32	28 mm
F2	0.46	0.60	23.33	1.30	16 mm
F3	0.44	0.56	17.00	1.27	14mm
F4	0.29	0.41	30.00	1.43	34mm
F5	0.25	0.35	30.00	1.43	34mm
F6	0.37	0.46	20.00	1.25	34mm

Figure 4.1: Bulk Density.

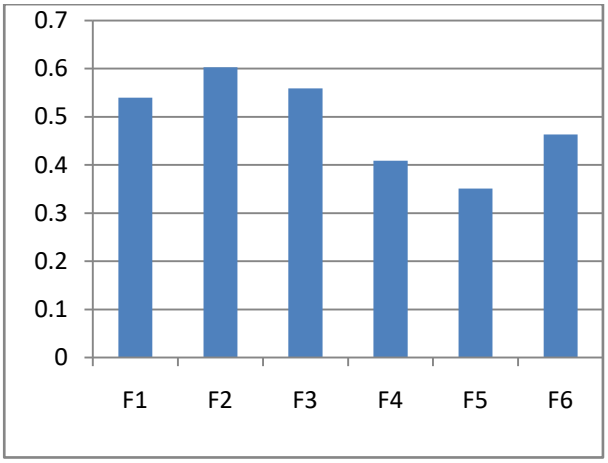

Figure 4.2: Tapped Density.

Figure 4.3: Carr's Index.

Figure 4.4: Hausner Ratio.

Figure 4.5: Flodex equipment

Variation of tablet weight:

The compressed mass must flow easily to form a small variation in tablet mass. Average tablet weight of the formulations found of all the trial runs had a range of 350 mg ±5 as shown in (Table 4.2). Slight variations related to the tablet weight could be due to differences in the bulk density in the formulations and poor flowability impacted on weight variations in all formulation (Figure 4.5). The variations were evident according to IP as shown in (Tablet 3.2) and within the limit for lyophilized mannitol 5± and out of range for the rest of formulations as shown in (Table 4.2).

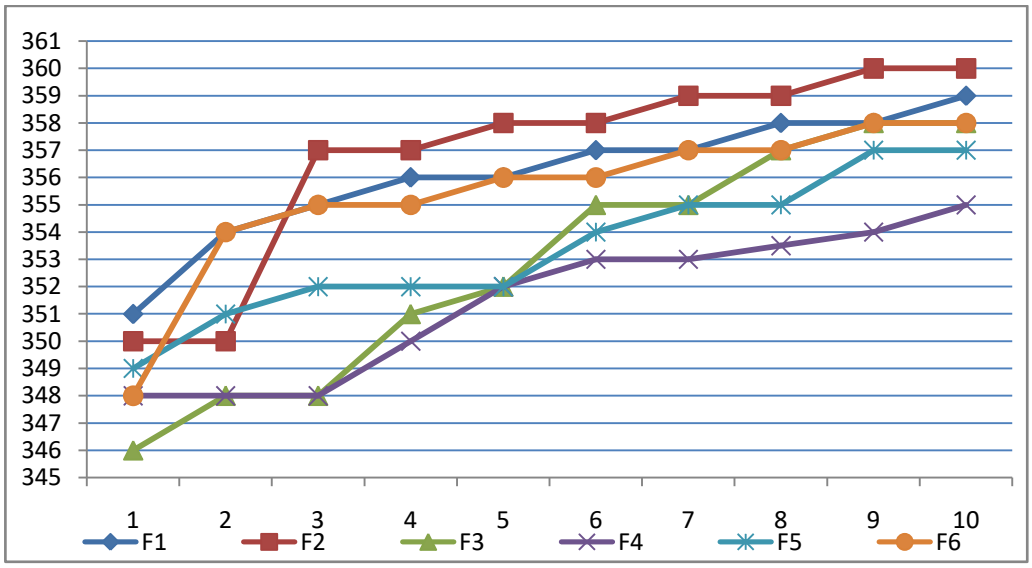

Figure 4.6: Weight Variations of ODT Formulations.

Tablet Thickness:

We divided formulations into two groups according to diameter of single press that we used in trails, formulations A were compacted in diameter 10 mm and the thicknesses were ranging from 5.05 mm to 5.35 mm as shown in (Table 4.2) and (Figure 4.6), and formulations B were compacted in diameter 12 mm and thickness were ranging from 3.40 mm to 3.68 mm as shown in (Table 4.2) and (Figure 4.7). All the formulations of ODT showed less deviation in thickness.

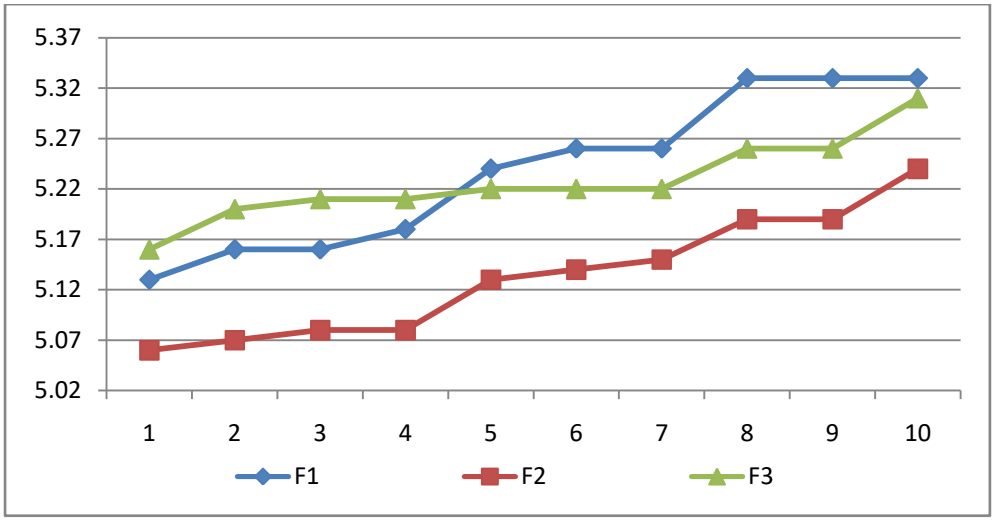

Figure 4.7: Thickness of ODT Formulations (A).

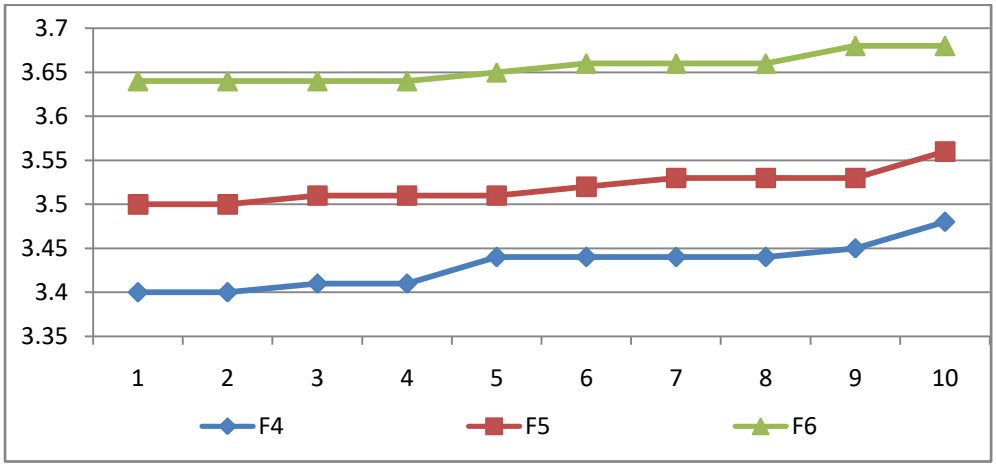

Figure 4.8: Thickness of ODT Formulations (B).

Tablet Hardness:

The hardness varied from 41±2 to 43±3 N as shown in (Figure 4.7). Acceptable hardness was achieved in almost all the formulations as shown in (Table 4.2).

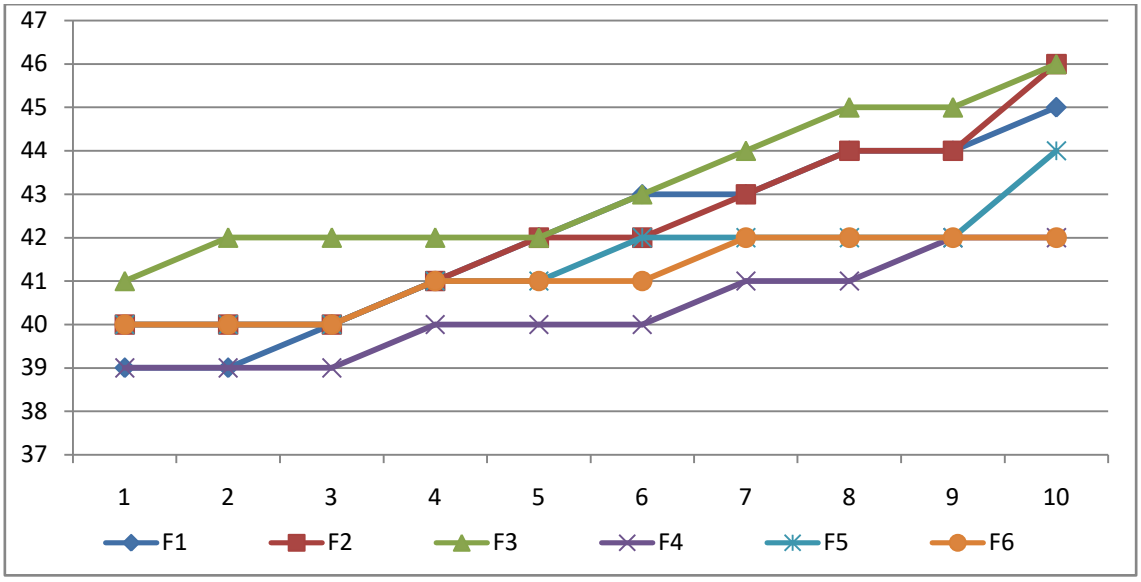

Figure 4.9: Hardness of ODT Formulations.

Tablet Friability:

The friability was found to be below 1% which was an indication of good resistance of tablets as shown in (Table 4.2) and (Figure 4.8).

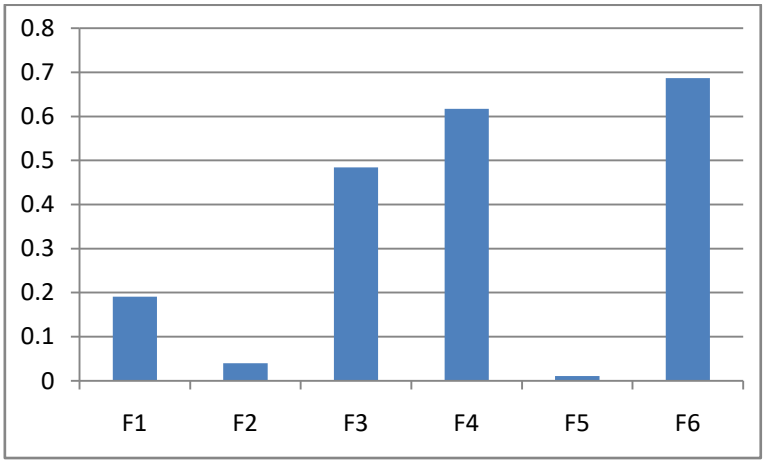

Figure 4.10: Friability of ODT Formulations.

Disintegration Time of Tablet:

A short disintegration time and sufficient mechanical strength are important factors for an ODT formulation. According to FDA definition of disintegration time for ODTs is < 30 seconds in all formulations disintegration times were within limit in ranging 16s to 27s as

shown in (Figure 4.9). The lowest disintegration time was 17±1 s for F5 and 23±3 s for F1 respectively, as shown in (Table 4.2).

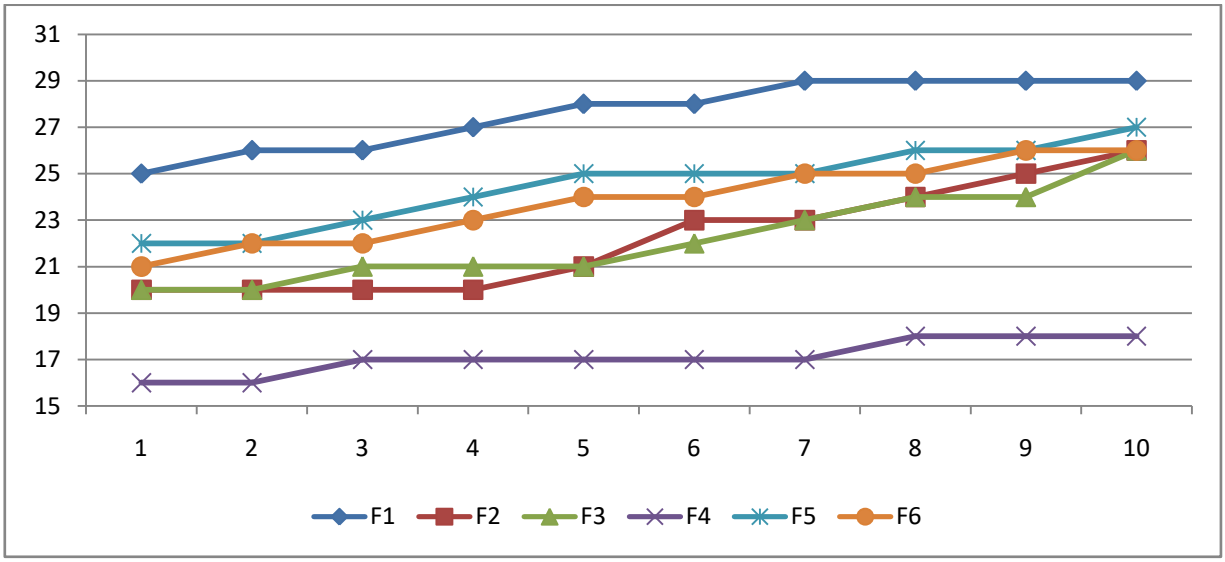

Figure 4.11: Disintegration Time of ODT Formulations.

Table 4.2: The Evaluation of Ascorbic Acid ODT Data.

Ingredient (mg/tablet)	Formulation					
	F1	F2	F3	F4	F5	F6
Weight (mg)	355±4	355±5	353±3	351±3	352±4	353±5
Hardness(N)	42±3	43±2	43±2	41±2	43±2	41±1
Thickness(mm)	5.23±0.10	5.15±0.08	5.13±0.07	3.44±0.04	3.53±0.03	3.66±0.02
Disintegration (s)	27±2	23±3	23±3	17±1	25±2	23±2
Friability (%)	0.19	0.04	0.48	0.62	0.01	0.69

Palatability Evaluation for Tablet:

The satisfying taste is the critical issue in ODT formulation in order to improve patient compliance. The results of this study are worthy, and the limitation in this study is that volunteers were healthy young adults and their decision may not be as same as of elderly patients. So it would be of great importance to assess the palatability of these ODTs in such elderly patients. In this study we found that mannitol can't effectively mask the unpleasant taste and mouth feel depending on mannitol grades such as bitterness and unpleasant taste. And the evaluation was from high scale to lower F4 ≥ F1 > F3 > F2 > F1 > F6. According to that F4 and F1 had from good to acceptable taste with smoothness mouth feels.

Table 4.3: Palatability Evaluation.

	F1		F2		F3		F4		F5		F6	
Volunteer Number	taste	Mouth feels	taste	Mouth feels	taste	Mouth feels	Taste	Mouth feels	taste	Mouth feels	taste	Mouth feels
1	2	2	2	1	2	1	2	1	2	1	2	1
2	3	1	0	1	3	1	4	1	2	1	2	1
3	3	1	1	1	1	1	1	0	1	0	1	0
4	2	1	2	1	2	1	3	1	2	1	2	1
5	2	0	3	1	3	1	3	0	2	1	2	1

CHAPTER FIVE

CONCLUSION

5.1 Conclusion:

ODTs have potential advantages comparing to conventional dosage forms by improving patient compliance, convenience, bioavailability and rapid onset of action. They are the best choice for drug delivery to geriatric and pediatric patients. They have important advantages of both solid and liquid dosage forms, as they stay solid during storage, which aid in stability of dosage forms and transform into liquid form within few seconds after its administration. In the present study, the impact of the different grades of mannitol as well as the effect of lyophilized mannitol and ascorbic acid on the orally disintegrating tablets was studied. It was concluded that the inner pore morphology of the freeze-dried mannitol is of major significance for disintegration time. Even though it was possible to develop an ODT formulation with sufficient mechanical strength and faster disintegrating time by using lyophilized mannitol and ascorbic acid, the taste and moth feels presented challenges and therefore it is suggested that such problems should be overcome by adding flavoring agents or particle coating if further improvement of the ODT formulation developed in this study is desired.

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