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ORALLY DISINTEGRATING TABLET

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ABSTRACT
Orally disintegrating tablets (ODT) have emerged as one of the popular and widely accepted dosage forms especially for pediatric and geriatric patient. ODT have gained considerable attention as preferred alternative to conventional tablet and capsule formulation. Various scientific technique including freeze drying, molding, spray drying, direct compression, etc. have been employed for the development of ODT. These techniques render the disintegration of tablet rapidly and dissolve in a mouth without chewing or additional water intake. The purpose of this study is focused on freeze drying method and compression ascorbic acid and lyophilized ascorbic acid as a API and various form of mannitol (powder, granule, spray dry, lyophilize) as a sweetener to mas unpleasant mouth feel to achieve better taste. The result showed that have given different influence on evaluation taste. The spray dried mannitol provides good flowability but lyophilized offers low flowability. The lyophilized method has decreased dissolution and disintegration time, but the taste has not affected by lyophilized method. Finally, mannitol cannot prevent uninteresting taste of the tablet.

KEYWORDS: Orally disintegrating tablet, flowability, disintegrating, freeze drying, mannitol, leophilized method.

INTRODUCTION
Orally disintegrating tablet(ODTs) should disintegrate in the mouth without additional water or with a very small amount (e.g., 1–2 mL) of water. A disintegration fluid is provided by the saliva of the patient. A disintegrated tablet should become a soft paste or liquid suspension, which can provide good mouth feel and smooth swallowing. Orally disintegration usually means disintegration of tablets in less than 1 minute, but it is preferred to have disintegration as soon as possible (Li et al.,2006).

Because ODTs dissolve or disintegrate in the patient's mouth, the drug will be partially dissolved in close proximity to the taste buds. After swallowing, there should be minimal or no residue in the mouth. A pleasant taste inside the mouth becomes critical for patient acceptance. Unless the drug is tasteless or does not have an undesirable taste, taste-masking techniques should be used. An ideal taste-masking technology should provide drugs without grittiness and with good mouth feel. Amount of taste masking materials used in the dosage forms should be kept low to avoid excessive increase in tablet size. Taste masking of bitter tasting drugs is critical to the success of the ODT formulations (Pondell R, 1996).

The degree of ease when taking a tablet depends on its size. It has been reported that the easiest size of tablet to swallow is 7-8 mm while the easiest size to handle was one larger than 8 mm. Therefore, the tablet size that is both easy to take and easy to handle is difficult to achieve. Drugs having ability to diffuse and partition into the epithelium of the upper GIT (log P > 1, or preferable > 2); and those able to permeate oral mucosal tissue are considered ideal for ODT formulations (Szakonyi et al., 2013).

The fast dissolving property of the ODTs requires quick ingress of water into tablet matrix thus requires some basic approaches such as maximizing the porous structure of the tablet, incorporation of suitable disintegrating agent and use of highly watersoluble excipients in the formulation. Excipients use in ODTs contain at least one super-disintegrant (having mechanism of wicking, swelling or both), a diluent, a lub- ricant and optionally a swelling agent, a permeabilizing agent, sweeteners and flavorings (Kumar et al., 2012; Beri and Sacher, 2013). Important criteria for excipients would be used in the formulation of ODTs can be identified as ability of disintegrates quickly, not interfere in the efficacy and organoleptic properties of the ODTs due to individual properties, not interact with drug and other excipients, do not negatively affect the

desired final integrity and stability of the product and having melting points of range between 30-350C (Bandari et al., 2008; Ratnaparkhi et al., 2009; Bharawaj et al., 2010; Bhasin et al., 2011; Thakur and Narwal, 2012). There are number of techniques generally employed in the formulation of orally disintegrating dosage forms. These techniques have their own advantages as well as disadvantages and are described below:

Solid dosage form facilitates and overcome many disadvantages above another type of dosage forms

1.Accurate dose. 2. Protection e.g. coated tablets, sealed ampoules. 3. Protection from gastric juice. 4. Masking taste and odor. 5. Placement of drugs within body tissues. 6. Sustained release medication. 7. Controlled release medication. 8. Optimal drug action. 9. Insertion of drugs into body cavities (rectal, vaginal) 10. Use of desired vehicle for insoluble drugs.

It is not just the active pharmaceutical ingredient (API) that is of concern in pediatric formulations. In order to have a successful formulation, a wide range of functional excipients are also included in the formulation. The choice of which will be determined by the dosage form and delivery method. Despite the traditional point of view that declares excipients are inert, no substance is completely free from toxicity. Since excipients generally represent a substantial share of a formulation's composition, some caution must be considered to choose excipients that offer as the least harm to the patient as possible. With benzyl alcohol which is a commonly used preservative in instance, its metabolism to hippuric acid which can be readily excreted, is decreased in neonates leading to high toxicity (Nahata, 2009) due to pharmacokinetic differences altering their administration, distribution, metabolism and elimination when compared to adults (Nahata, 3 2009).

Published guidelines concerning the use of excipients in pediatric formulations (van Riet-Nales, 2012) declare that choosing of excipients for pediatrics formulations should be accomplished with special care and also with consideration of different sensitivities between alternative age groups. The inclusion of any excipient in a formulation has to be justified by considering its function and also should be included at the least possible concentration for the desired effect. Inclusion should also be promoted using as much data from toxicological rate, scientific guidelines, food legislation and literature as possible. Information about compatibility of excipients with the active and with other excipients should be revealed. It is also agreed that any new excipient be examined in preclinical and clinical trials to assure about safety. No organization can recommend the conductance of ADME studies over the entire pediatric group, despite pediatrics being a target population (Fabiano et al, 2011). The purpose of this study is focused on freeze drying method and compression ascorbic acid and lyophilized ascorbic acid as a API and various form of mannitol (powder, granule, spray dry, lyophilize) as a sweetener to mas unpleasant mouth feel to achieve better taste.

MATERIAL AND METHODS

Materials: Mannogem powder (mannitol powder), Mannogem EZ (Mannitol spray dried), Mannogem granular (Mannitol granular) was obtained from (SPI pharma). Mannitol lyophilized was synthesized in near east laboratory. Ascorbic acid was obtained from (ZAG Kimya). Avicel PH-102 (microcrystalline cellulose) (MCC) was obtained from (FMC corp.).AC-DI-SOL (Croscarmellose sodium croslinked) was obtained from (IMCD). Sodium lauryl sulphate was obtained from (Emirkimya). Aerosil (Silicon dioxide) was obtained from (ZAG kimya). Polyethylene glycol 4000 (PEG 4000).

Freezing step: Freezing is the first step of freeze-drying. During this step, material dissolved and stirred in a water bath (BUCHI) at 30 C° for 20 minutes, then followed bythe liquid suspension was cooled at -18°C, and ice crystals of pure water formed. The primary drying stage was carried out using an (Christ-ALPHA 1-4 LD PLUS) and involved sublimation of ice from the frozen product.

Prepare 100g of lyophilize ascorbic acid by freeze drying: At first, boiling flask was washed by methanol and dried it into the autoclave. To prepare ascorbic acid solution, 100 g of powder ascorbic acid was weighted by electrical balance. Then, ascorbic acid powder was poured to 1000ml boiling flask. 500ml distal water was determined by graduated cylinder and poured faucet slowly to 1000ml boiling flask. Later, solution was stirred by hand and put on the water 59 bath. The temperature of was set heater at 30C° and fixed the temperature at 30C°. Speed of rotation was set at 3 rpm and waited for 20 minutes. After that, sample was put in the refrigerator to freezing at -18 C°. Finally, the ascorbic acid powder dissolved completely and got clear solution (figur3.3).

Prepare 100g of lyophilize mannitol by freeze drying: At first, boiling flask was washed by methanol and dried it into the autoclave. To prepare ascorbic acid solution, 100 g of powder mannitol was weighted by electrical balance. Then, mannitol powder was poured to 1000ml boiling flask. 500ml distal water was determined by graduated cylinder and poured faucet slowly to 1000ml boiling flask. Later, solution was stirred by hand and put on the water bath. The temperature of was set heater at 30C° and fixed the temperature at 30C°. Speed of rotation was set at 3 rpm and waited for 20 minutes. After that, sample was put in the refrigerator to freezing at -18 C°. Finally, the mannitol powder dissolved completely and got clear solution (Figur 3.2).

Prepare 100g of lyophilize mannitol and ascorbic acid by freeze drying: At first, boiling flask was washed by methanol and dried it into the autoclave. To prepare ascorbic acid solution, 50 g of powder ascorbic acid and

50g powder mannitol weighted by electrical balance. Then, mannitol powder and ascorbic acid was poured to 1000ml boiling flask. 500ml distal water was determined by graduated cylinder and poured faucet slowly to 1000ml boiling flask. Later, solution was stirred by hand and put on the water bath. The temperature of was set heater at 30C° and fixed the temperature at 30C°. Speed of rotation was set at 3 rpm and waited for 20 minutes. After that, sample was put in the refrigerator to freezing at -18 C°. Finally, the mannitol powder dissolved completely and got clear solution.

RESULTS AND DISCUSSION

Using lyophilized mannitol and comparing it with current mannitol forms (granular, powder, and spray-dried) and also employing ascorbic acid as an API an ODT formulation were presented in the present research study. For improvement of the ODT taste, Mannitol was employed as the taste masking. It is highly crucial to obtain a formulation which yields good taste, stiffness, being well-shaped, delicate and quick disintegration ODTs.

Since preparation of direct compression is easy and it is economical, so it was employed as the main research method (Medina and Kumar, 2006). Furthermore, since tablet is quickly disintegrated, enjoying convenient stiffness and delicacy, so it was also used in this study (Bi et al., 1999). Findings of the study were highly convenient in terms of fast disintegration, tablets' size and taste. However, pitfalls including inappropriateness for low solvable powder which causes change in the product weight might influence stiffness and delicacy. Moreover, static charge in the time of mixing and compaction process might cause accumulation of the final product. ODTs formulation highly relies on the super-disintegrants' type, mechanism and mode. One of such super-disintegrants is Croscarmellose Sodium (Ac-Di-Sol SD-711), which is added to the formulation during the underlying process. In general, super-disintegrants are employed in order to prepare ODTs or to return the disintegrating tablets into their initial manner. They are applied in ratio of 10%-20% of the ODT weight. Such percent might also vary in some cases. Hence, selection of the best super-disnintegrant is highly crucial, when preparing ODT formulation in direct compression method (Camarco et al., 2006). It also, should be noted that the super-disintegrant's compaction is of great importance in this process. It is suggested that the prepared ODT formulations to have lower stiffness, since the pores inside a range accelerate disintegration process of the tablet, however the porosity feature of the tablets might reduce efficiency of the disintegrating agents functioning with swelling mechanisms. Croscarmellose Sodium was employed in this investigation due to its functioning manner under swelling and wicking processes. Since micro crystalline cellulose (Avicel PH-102) shows higher adjustment to low compressibility due to its plasticity nature and also as it shows no sensitivity to lubrication in formula, so it was employed as direct compression diluents in the current study. As can be seen in (Table 3.1) different grades of Mannitol were employed in the present research in order to promote taste of ODT tablets. Mannitol with its compatible features such as non-hygroscopic, sweetness, cooling effects, crystal forming agents during lyophilization stages, is the best choice for the objective of our study. These features impede it of sudden disintegration, freeze drying and interaction with fluids. High blood pressure is not observed in mannitol metabolism. When using different grades of mannitol in ODT formulations, the scholars confronted various difficulties such as flowability, compaction and need for lubrication agents

Flow features

Bulk density (see Figure 4.1), tapped density (see Figure 4.2), Carr's Index (see figure 4.3) Hausner Ratio (Figure 4.4) and Flodex equipment (Figure 4) were, respectively, used to investigate ODT flow features. Findings of the investigation indicated range of 0.27±0.02 to 0.45±0.02 g/ml for bulk density, 0.35±0.01 and 0.55±0.15 g/ml for tapped density, 17% - 30% range for Carr's Index. These cases can be seen in the (Table 4.1). Investigation of the pre-formulation carried out on powder in terms of flow features indicated range of above 17% for Carr's index. Solvability low flow was observed in all of the implemented formulation. After investigation of the features it was shown that compared to mannitol powder granular and lyophilized (Table 4.1) spray-dried mannitol indicated higher flow and compaction possibility.

Table 1: Flow and compaction features.

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

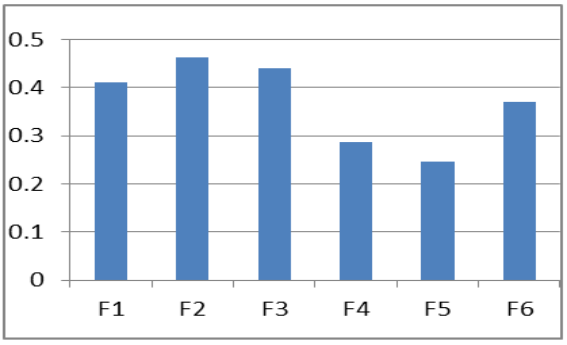

Figure 1.1: Bulk density.

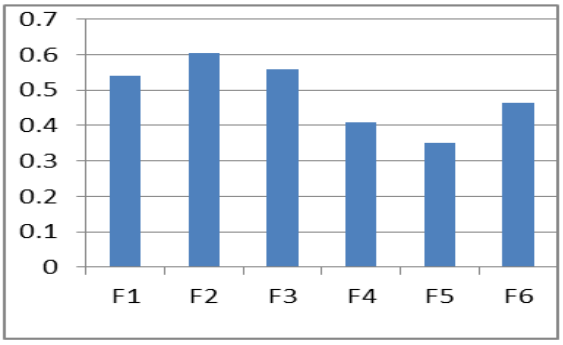

Figure 1.2: Tapped density.

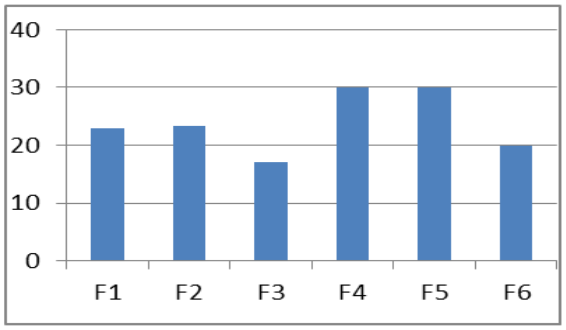

Figure 1.3: Carr's index.

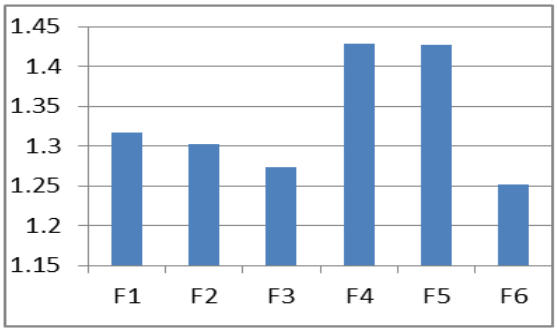

Figure 1.4: Hausner ratio.

Changes in tablet weight

When preparing the tablet, its compacted mass should flow with ease in order to make a small change in its mass. As it can be seen in the table 4.2 the average tablet mass was obtained as 350 mg ±5 in all tests. Differences in bulk density and poor flowability might influence slight changes in the tablet mass through all formulations (figure 4.5). Such changes were observed in the IP seen in the (Table 3.2), in the lyophilized mannitol range of 5± and beyond the range for the remaining formulations shown in (Table 4.2).

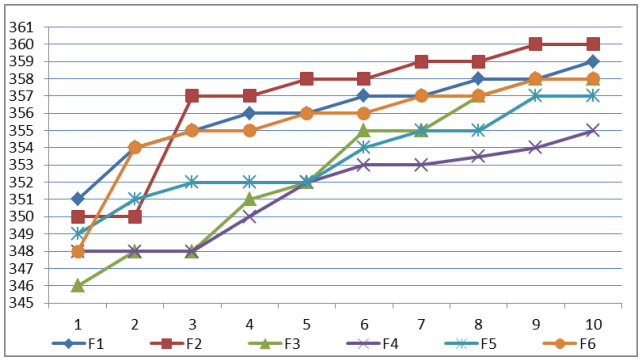

Figure 2: Mass changes of ODT formulations.

Thickness of the tablet

Based on the diameter of single press employed in the tests, the formulations were divided into two groups. Tablets of formulation A involved those with 10 mm in diameter and thickness of 5.05-5.35 mm. This can be seen in the table (4.2) and Fig. (4.6). On the other hand, tablets of formulation B involved those with diameter 12 mm and thickness of 3.40 mm- 3.68 mm. This can be seen in the Table (4.2) and Fig (4.7). A slight deviation in thickness was observed in all ODT formulations.

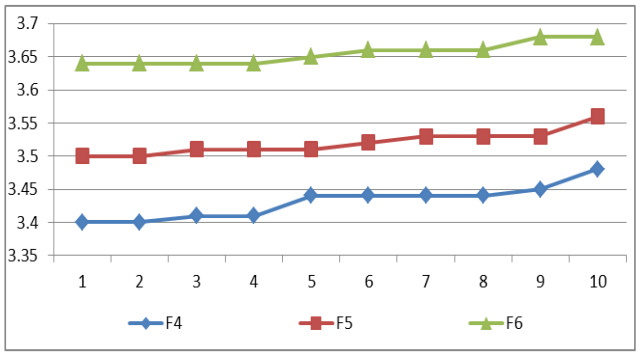

Figure 3: ODT thickness formulations (B).

Tablet Stiffness

As can be seen in the (Fig.4-7) the tablets' stiffness changed from 41±2 to 43±3 N. The permitted stiffness was obtained for almost all of the formulations. This can be seen in (Table 4.2).

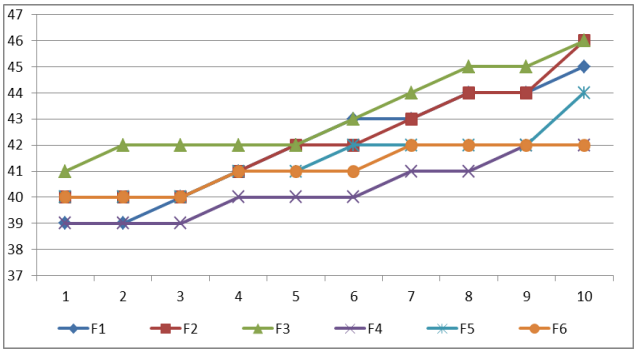

Figure 4: Stiffness in ODT formulations.

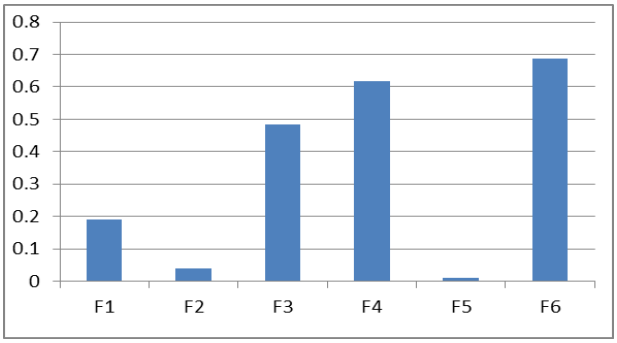

Figure 5: Delicacy of ODT formulations.

Disintegration Speed of the Tablet

In an ODT formulation two factors are of great importance; firstly, it should enjoy rapid disintegration and secondly, it should have enough mechanical strength. Food and Drug Administration (FDA) mentions that the optimal disintegration time interval for an ODT is < 30 seconds for all formulations being in the time range of 16s- 27s. This has been shown in the (Figure 4.9). As it can be seen in the table 4.2 the lowest disintegration time interval was obtained as 17±1 s for F5 and 23±3 s for F1 respectively.

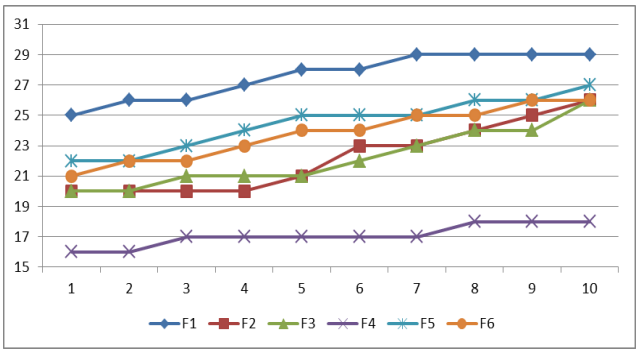

Figure 6: ODT Disintegration time interval formulations.

Table 2: Results of ascorbic acid evaluation for 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
Stiffness (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
Delicacy (%)	0.19	0.04	0.48	0.62	0.01	0.69

The tablet Taste evaluation

To be more convenient with the patient, a tablet needs to have a satisfactory taste in its ODT formulation. Present research study obtained some valuable findings; however it should be noted that the test was conducted on a group of young adults and this can be considered as one of its limitations. Since, if the test is to be conducted on a group of elderly patients, the results might be different, because the decisions made by the two groups might be completely different. So it is proposed to evaluate taste of the underlying ODTs on the latter group, too. Findings of the study indicated that mannitol cannot prevent uninteresting tastes of the tablet (such as bitterness and some other unpleasant tastes) regardless of its rate and grade. The taste evaluation was conducted from higher grade to lower as F4 ≥ F1 > F3 > F2 > F1 > F6. Results of the investigation indicated that F4 and F1 scales showed good to palatable taste along with smoothness feeling in mouth.

Table 3: Taste 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

CONCLUSION

Compared to ordinary dosage forms, ODTs show better efficiency in terms of improvement in compatibility, convenience and fast disintegration. These are considered as the best drug cases for old and child patients. These drugs enjoy various strong points such as

being available both in solid and liquid forms. In terms of being solid they can remain in their solid form during storage and this helps longer stability of the dosages forms. On the other hand, they can easily change into liquid short after being used with water or other liquids. Present study proceeded on investigation of the effects of grades of mannitol, mannitol and ascorbic acid on orally disintegrating tablets. Findings of the study revealed that porosity of the freeze-dried mannitol is highly important in disintegration time. It is also worth mentioning that addition of lyophilized mannitol and ascorbic acid might result in development of ODT formulation with enough mechanical strength and short disintegration time, but it causes bad taste and feeling inside mouth. Hence, it is proposed to use flavors or particle coatings in this field to solve the palatability problem, if more improvement in ODT formulation is expected.

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