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Effect of Mannitol on Physical Characters of Lyophilized Fast-Disintegrating Tablets

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ABSTRACT

Objectives: Fast-disintegrating tablets (FDTs) also known as orally-disintegrating tablets, orodispersible tablets, fast-melting tablets, rapid-melt tablets are a relatively new dosage form. They are tablets that when placed in the mouth, disintegrate upon coming in contact with the saliva without further need for water or chewing to be swallowed. In order to achieve fast disintegration, tablets are formulated to be highly porous, which unfortunately greatly reduces the mechanical strength of the tablets. The main challenge in formulating FDTs is achieving a balance between fast disintegration and good mechanical strength. **Methods:** The formulation of, lyophilized fast-disintegrating tablets (LFDTs) is comprised of mainly a binder e.g. gelatin, a lyoprotectant as glycine, as well as mannitol a bulking agent and disintegration enhancer for the manufacture of LFDTs. The effect of mannitol concentration on physical characters of LFDTs, namely, friability, hardness and in-vitro disintegration time was investigated over the range of 10% to 70% *w/v*. Design-Expert® software v.7 (Stat-Ease Inc., Minneapolis, MN, USA) was used to analyze the obtained results. **Results:** It was observed that increasing mannitol concentration enhanced the mechanical properties of the LFDTs. Where, it decreased friability and increased hardness. The relationship between mannitol concentration and the *in-vitro* disintegration time was found to be parabolic. **Conclusion:** The study encouraged 40% *w/v* as an optimum concentration of mannitol for ultimate LFDTs formulation.

Keywords: *Fast-disintegrating tablet; Lyophilized tablet; Mannitol; Optimization of LFDTs; Physical characters of LFDTs*

INTRODUCTION

Fast-disintegrating tablets (FDTs) are tablets that disintegrate upon coming in contact with the saliva in the oral cavity without further need for water or chewing to be swallowed. The European Pharmacopoeia embraces the term orodispersible tablets for tablets that disperse or disintegrate within 3 minutes in the mouth before swallowing [1]. FDA-CDER Nomenclature Standards Committee developed the following definition for an orally-disintegrating tablet (ODT) as a new dosage form in 1998: "*A solid dosage form containing medicinal substances which disintegrates rapidly, usually within a matter of seconds, when placed upon the tongue*" [2]. Fast disintegration usually means the disintegration of tablets in less than one minute, where it is preferred to have disintegration as soon as possible within 60 seconds [1]. FDTs combine the advantages of solid dosage forms like good stability, accurate dosing, and portability with the advantages of liquid dosage forms like ease of administration, which makes it especially suitable for people who suffer from dysphagia, travelling patients, patients with little access to water, bedridden or developmentally disabled patients. Moreover, ease of administration enhances patient

compliance. Additionally, when the tablet disintegrates in the mouth, a significant proportion of the drug may be absorbed from the buccal cavity and pre-gastric regions giving FDTs the advantage of avoiding the first pass metabolism and hence, improving the bioavailability, if the drug is significantly affected by hepatic metabolism and achieving a faster onset of action.

Fast-disintegrating tablets are prepared by various methods; lyophilization, direct compression and cotton candy (floss). Compared to other methods, the process of lyophilization is suitable for thermo-labile drugs. As well, it results in a highly porous structure, leading to fast liquid penetration and thus fast disintegration within seconds. Unfortunately, it also leads to tablets with poor mechanical strength.

The aim of the study was to investigate the effect of mannitol on the physical characters of lyophilized fast-disintegrating tablets with adequate mechanical strength.

MATERIALS AND METHODS

Gelatin from bovine skin (type B), glycine and mannitol were purchased from Sigma Aldrich, Germany. All aqueous solutions were prepared using distilled de-ionized water. All other chemicals were of analytical grades.

Preparation of lyophilized fast dissolving tablets (LFDTs)

A 2% *w/v* solution of gelatin was prepared by dissolving the appropriate amount of gelatin in deionized water, using a CG-1990-35 hot plate magnetic stirrer (Chemglass Life Sciences Inc., Vineland, NJ, USA) maintained at 37°C - 40°C and stirred at 350 rpm. Glycine was used at a constant concentration of 30% *w/v*. Then the appropriate amount of mannitol was dissolved in the mixture to prepare 10, 20, 30, 40, 50, 60 and 70% *w/v* solutions, formulations F1 – F7, respectively. Keeping the concentration of gelatin and glycine constant, the concentration of mannitol was varied to investigate the effect of mannitol on the LFDT.

An appropriate volume of the solution, equivalent to 400 mg total solid, were poured in each pocket of a polyvinyl chloride (PVC) blister pack , then the volume was completed to one mL with deionized water in order to keep the tablets weight and thickness constant across all formulations. They were then frozen in an Ultra-low freezer (Thermo Fisher Scientific, Waltham, MA, USA) at a nominal temperature of -80°C. Afterwards, they were freeze-dried using a Modulyo® lyophilizer (Edwards, Sussex, England) operated at a temperature of -40°C and pressure of 0.1 mbar (10 Pa) for 48 hours for the water to sublimate (primary drying) then at 20°C and 0.01 mbar (1 Pa) for 10 hours (secondary drying).

Evaluation of the prepared LFDTs

Measurement of thickness and diameter of LFDT

For measuring the thickness and diameter of LFDTs, six tablets were measured using a Mitutoyo 7301 dial thickness gauge, (Mitutoyo, Japan). Ten tablets were individually weighed and the average of tablets weight was calculated. Results are presented as average and standard deviation (±SD).

Friability, hardness and in-vitro disintegration time were measured for the seven prepared formulations according the United States Pharmacopeia (USP-35) [3].

Friability

Friability testing was used to determine the resistance of the tablets to the mechanical stress experienced during manufacturing, packing and transportation using Erweka Friabilator, type PTF1 (Pharmatest, Hainburg, Germany). According to USP 35 [4], a sample of whole tablets corresponding to 6.5 g was placed in the drum of the friabilator. The drum was rotated at 25 rpm for 4 minutes, after which the tablets were removed, dedusted and reweighed. Unless there are broken tablets in the sample, the test is run once, otherwise the test is repeated twice and the mean of the three tests is determined. The friability of the tablets is expressed as percentage weight loss. A friability of not more than 1.0% is considered acceptable.

$$Friability, \% = \left(\frac{(initial\ weight - final\ weight)}{initial\ weight}\right) \times 100\% \qquad \text{eq. (1)}$$

Hardness

Tablet breaking force, more commonly known as tablet hardness, refers to the force required to break a tablet, as a measure of mechanical strength. According to USP 35 [5], the hardness of the tablets was measured using Dr. Schleuniger® Pharmatron hardness tester (Sotax AG, Aesch, Switzerland), where the tablet is placed across its diameter between two platens, one of which is moving. A minimum of 6 tablets were tested and the average was calculated.

In-vitro disintegration time

The disintegration time refers to the time taken for the tablet to completely disintegrate until any residue left is a soft mass. Disintegration time was determined using the DST-3 disintegration tester (Logan Instruments Corp., NJ, USA) operated according to USP 35 [6]. In-vitro disintegration time was determined for six tablets, tested individually for more accurate results, in simulated salivary fluid (SSF) without enzymes at pH 6.75 [7].

Table 1 Composition of Different LFDT formulations & their Responses

Formula	Composition of LFDTs			Responses		
	Gelatin (% w/v)	Glycine (% w/v)	Mannitol (% w/v)	Friability (%) (Y_1)	Hardness (kg) (Y_2)	Disintegration Time (sec) (Y_3)
F1	2	30	10	0.521 ±0.057	2.2 ±0.43	14.21 ±1.31
F2	2	30	20	0.478 ±0.092	3.1 ±0.18	9.64 ±1.20
F3	2	30	30	0.396 ±0.050	3.4 ±0.55	5.26 ±0.74
F4	2	30	40	0.302 ±0.046	3.7 ±0.34	4.33 ±0.56
F5	2	30	50	0.285 ±0.034	4.0 ±0.22	9.52 ±0.81
F6	2	30	60	0.201 ±0.078	5.2 ±0.13	12.11 ±1.11
F7	2	30	70	0.117 ±0.004	5.4 ±1.25	15.73 ±1.42

Data Analysis of Friability, Hardness & In-vitro Disintegration Time

Design-Expert® v10 software (Stat-Ease Inc., Minneapolis, MN, USA) was used to analyze the obtained results and provide polynomial equations that describe the relationship between the concentration of mannitol (X) and the three responses: friability (Y_1), hardness (Y_2) and disintegration time (Y_3). All models were statistically validated by the *p*-value of the model, coefficient of determination (R^2), adjusted R^2, predicted R^2, adequate precision and predicted residual sum of squares (PRESS) [8]. Box-Cox plots were used to find if transformation of the data was needed to improve normality and homogeneity of the data. Each response was checked for the presence of outliers using Cook's distance, D_i.

Moisture Content

Six tablets from each formulation were analyzed for their residual moisture content after lyophilization using Karl Fischer titrations carried out with 758 KF Titrino volumetric titrator (Metrohm AG, Herisau, Switzerland). Each tablet was inserted in the titration vessel containing dried methanol (Karl-Fischer grade) and titrated with Hydranal-Composite 5 reagent (Riedel-de-Haen, Seelze, Germany).

RESULTS AND DISCUSSION

RESULTS

Evaluation of the prepared plain LFDTs

The friability, hardness and in-vitro disintegration time results for the seven formulations were entered into the Design-Expert® software for data analysis. The results are shown in Table (1).

Diameter and thickness determination

The aforementioned procedure resulted in tablets with 7.907 mm ±0.078 diameter and 2.472 mm ±0.263 thickness. The average weight was 402.455 mg ±3.940. Ten tablets were used from each formulation.

Friability

Table 1 shows that, the % friability values of LFDT formulations were decreased with the increase in mannitol concentration, F1 > F2> F3> F4> F5> F6 > F7.

Hardness

As shows in **Table 1**, hardness of LFDT formulations were observed to be increased with the increase in mannitol concentration.

In-vitro disintegration time

The effect of mannitol concentration on the in-vitro disintegration times of LFDTs were illustration in **Table 1**. It is obvious that the disintegration times decreased with the increase in mannitol concentration up to (F4) with 40% mannitol. After which, increase in mannitol concentration caused an elevation in the in-vitro disintegration times.

Data analysis of friability, hardness & in-vitro disintegration time

The Design-Expert® software was used to fit the obtained results to polynomial models. The *p*-values were <0.0001, 0.0002 & <0.0064 for friability (Y_1), hardness (Y_2) and in-vitro disintegration time (Y_3) respectively, indicating the significance of the model. The generated polynomial models also showed high R^2 values proving strong correlation, good agreement between the adjusted R^2 and the predicted R^2,

Table 2: Statistical parameters for the responses: friability (Y_1), hardness (Y_2) and in-vitro disintegration time (Y_3)

Statistical parameter	Response		
	Y_1	Y_2	Y_3
model *p*-value	< 0.0001	0.0002	0.0098
R^2	0.9865	0.9547	0.9012
adjusted R^2	0.9838	0.9456	0.8518
predicted R^2	0.9767	0.9192	0.6118
Adequate precision	40.574	21.775	11.891

an adequate precision more than 4 indicating high signal-to-noise ratio i.e. adequate signal. The statistical parameters for the three responses are shown in **Table 2**. The Box-Cox plots for any of the responses suggested no data transformations and no outliers were detected.

Polynomial equations in terms of coded factors for the measured responses are shown in equations (2) – (4). The coded equations are used as the predictive model for interpretation purposes.

$$Y_1 = +0.60 - 0.67\,X \quad \text{eq. (2)}$$

$$Y_2 = +1.80 + 5.14\,X \quad \text{eq. (3)}$$

$$Y_3 = +20.73 - 78.93\,X + 104.81\,X^2 \quad \text{eq. (4)}$$

The magnitude and sign of the coefficients of the mannitol concentration (X) in the polynomial equations (2) to (4) are used to deduce the effect of their respective terms. A larger coefficient indicates more influence of the independent factor on the response. A positive sign of coefficient indicates a positive effect i.e. an increase in (X) by one unit will cause a mean increase in the response by the value of the regression coefficient. While a negative term indicates a negative effect on the response i.e. an increase in (X) by one unit will cause a mean decrease in the response by the value of the regression coefficient [9]. The presence of the quadratic term indicates the existence of a parabolic relationship.

Moisture Content

The average moisture content (n=6) was 4.602% ± 0.048 - 3.723% ±0.069 for the formulations F1 - F7.

DISCUSSION

Data Analysis of Friability, Hardness & In-vitro Disintegration Time

The formulation of a LFDT includes a binder e.g. gelatin, a lyoprotectant e.g. glycine and bulking agent e.g. mannitol. The gelatin fibers form crosslinks and interchain H-bonds, leading to a firm and extensive 3D network structure[10].

The effect of X on Y_1

Equation (2) and **Figure 1** illustrate the effect of mannitol concentration (X) on the friability (Y_1). The linear equation has a coefficient (-0.67) and an intercept (+0.60). As shown in **Figure 1** indicates that an increase in mannitol causes a decrease in friability. Hawe & Friess (2006) confirmed that mannitol undergoes crystallization during lyophilization into α, β and δ forms that are more stable than the amorphous form, which makes it an appropriate bulking agent. This crystalline bulking property results in elegantly formed LFDTs with enhanced mechanical strength[11].

Mannitol's crystallinity allows drying to be performed at higher temperatures in shorter times without structural collapse of the tablet. The sublimation of ice leaves mannitol in a crystalline state, which provides the scaffolding necessary to maintain the integrity of the tablet[12].

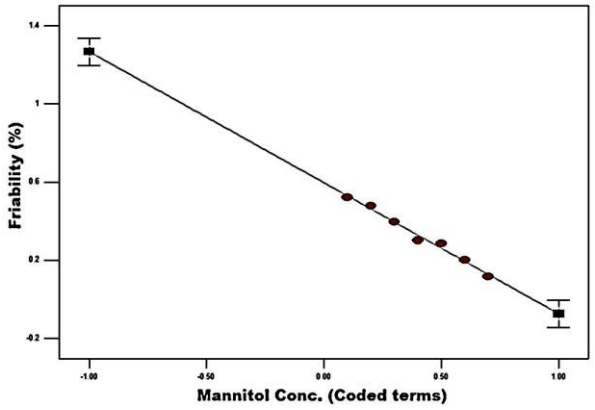

Figure 1: Relationship of mannitol concentration (in coded terms) vs. LFDT friability (%)

The effect of X on Y_2

Figure 2 and Equation (3) show the effect of mannitol concentration on hardness. The relationship between mannitol concentration and hardness is linear

with a coefficient of (+5.14) and an intercept of (+1.80), as mannitol concentration increases, LFDT hardness increases. As proven by AlHusban *et al.* (2010) that, during the lyophilization process, mannitol changes into a crystalline state. This crystalline state supports the tablet's matrix structure and improves the tablets' hardness[10].

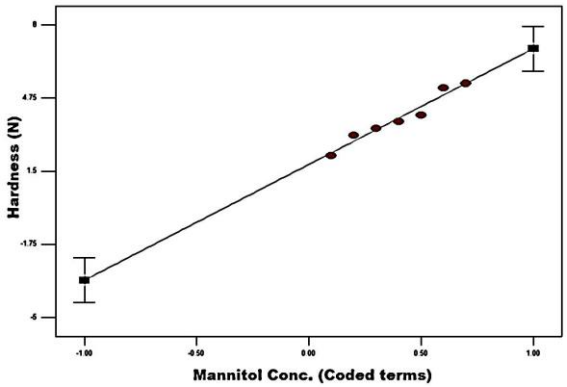

Figure 2: Relationship of mannitol concentration (in coded terms) vs. LFDT hardness (kg)

The effect of X on Y_3

The relationship between the concentration of mannitol (X) on the in-vitro disintegration time (Y_3) is shown in Equation (4) and **Figure 3**. As shown by the quadratic equation, the relationship between the disintegration time and mannitol concentration is parabolic. The disintegration time decreases with increasing mannitol concentration up to 40% *w/v* concentration, after which, increasing mannitol concentration causes an increase in the disintegration time, **Figure 3**.

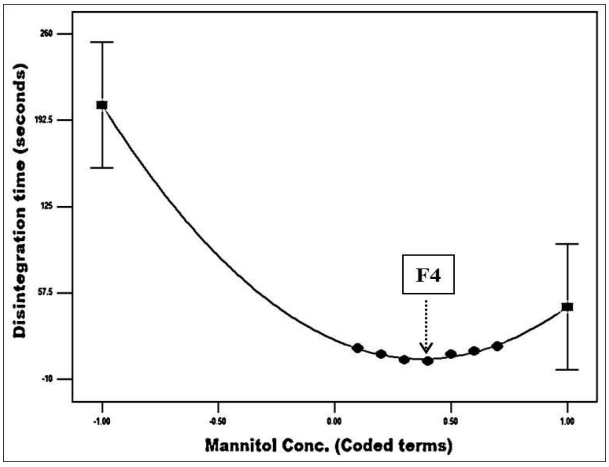

Figure 3: Relationship of mannitol concentration (in coded terms) vs. LFDT in-vitro disintegration time (seconds)

This relationship could be explained by the disintegration mechanism of the LFDTs. A 3D gel network is formed upon freezing of the gelatin solution, trapping water molecules inside. Where, disintegration of LFDTs occurs by "wicking"; drawing in of liquid into the tablet by capillarity and thus weakening of the intermolecular bonds holding the excipients' molecules together[13]. Accordingly, the tablet's hydrophilicity and porosity are the major factors that affect disintegration time [14]. Addition of mannitol increases the hydrophilicity of the tablet's matrix but, at the same time, decreases the porosity. Therefore, there is an optimal concentration of 40% *w/v* mannitol where a balance between hydrophilicity and porosity is reached, consequently giving the fastest disintegration time.

Moisture Content

The low moisture content in all formulations was below 5% indicating that lyophilization procedure was effective in removal of water from the tablets with predicted stability. The decrease in moisture content as mannitol concentration increases can be attributed to mannitol's crystallinity that allows more drying of the tablet.

CONCLUSION

The relationships between the physical characters of LFDTs (friability, hardness and *in-vitro* disintegration time) and the concentration of mannitol were established. Where, the study revealed 40% *w/v* as an optimum concentration of mannitol for ultimate LFDTs formulation.

Conflicts of interest

The authors declare that there is no conflict of interest. This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

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