Application of general multilevel factorial design with formulation of **fast disintegrating tablets containing croscaremellose sodium and Disintequick MCC-25**

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Abstract

Despite the popularity of orally fast disintegrating tablets (FDTs), their formulation can sometimes be challenging, producing tablets with either poor mechanical properties or high disintegration times. The aim of this experiment was to enhance the properties of FDTs produced by direct compression to have both sufficient hardness to withstand manual handling, and rapid disintegration time. General multilevel factorial design was applied to optimise and evaluate main and interaction effects of independent variables i) disintegrant concentration, ii) % filler (Disintequick MCC-25) to mannitol on the responses hardness, tensile strength and disintegration time. In this experiment mannitol was used as a diluent, Disintequick MCC-25 was termed as a filler and croscaremellose sodium was used as the superdisintegrant. Seven formulations were prepared following a progressive two-stage approach. Each stage involved the change in the ratio of excipients (Mannitol: Filler) (1:0), (1:0.25), (1:0.50), (1:1), (0.50:1), (0.25:1), (0:1) w/w and concentration of superdisintegrant (1%, 3%, 5%, 7%, 10% w/w). All FDTs were tested for different parameters such as diameter, hardness, tensile strength, thickness, friability and disintegration time. The results of multiple linear regression analysis show a good degree of correlation between experimental (R^2: 0.84, 0.94, 0.91) and predicted response (R^2: 0.83, 0.96, 0.95) for hardness, tensile strength and disintegration time respectively. The optimum formulations (regarding disintegration time with acceptable hardness and friability properties) consisted of: (i) 5% w/w disintegrant and 20% w/w filler to mannitol, showing a disintegration time of 30 seconds and a hardness of 66.6 N (6.8 kg/cm^2) and friability of 2.2%; (ii) 7% or 10% w/w disintegrant with 33.33% w/w filler to mannitol, showing disintegration time of 84 (for 7% disintegrant) and 107 (for 10% disintegrant) seconds, hardness of 73.86 N (for 7% disintegrant) and 72.68 N (for 10% disintegrant) and friability of 1.44 (for 7% disintegrant) and 1.15% (for 10% disintegrant).

Keywords: fast disintegrating tablets, general multilevel factorial design, tablet hardness, tensile strength, disintegration time

1. INTRODUCTION

Orally fast disintegrating tablets (FDTs), also referred to as fast melt, quick melt, oro-disperse, rapidly disintegrating, among others (Nagar et al., 2011; Rao et al., 2012; Deshmukh et al., 2012) are according to the US Food and Drug Administration (FDA) a "solid dosage form containing medicinal substances which disintegrate rapidly within a matter of seconds, when placed upon the tongue" (FDA., 2008). The European Pharmacopeia describes them as "uncoated tablets intended to be placed in the mouth where they disperse rapidly before being swallowed" it is also stated that the disintegration time is within 3 minutes (British Pharmacopoeia., 2013).

FDTs provide patients with an effective alternative for taking their medication. They compensate many pharmaceutical and patient's needs (Abay and Ugurlu., 2015), particularly paediatric, geriatric and bedridden patients, patients with dysphagia, or even for those who are travelling and have little or no access to water (Nagar et al ., 2011; Arora and Sethi, 2013; Abay and Ugurlu, 2015; Sharma et al., 2012). FDTs disperse or dissolve in the saliva, this leads to pre-gastric drug absorption of the tablets. As a result, FDTs have greater bioavailability than that observed from conventional tablet or capsule dosage forms and avoid first metabolism which can be advantageous (Jeong et al., 2008; Hirani et al., 2009; Nagar et al., 2011; Sharma et al., 2012). For these reasons, over the past three decades FDTs have gained considerable attention (Abay and Ugurlu., 2015) and have been the favourite development of product development scientists for facilitating ease of medication (Nagar et al., 2011).

Despite the popularity of FDTs, their formulation can sometimes be challenging. FDTs are made of very porous and soft moulded matrices or compressed into a tablet with very low compression force (Deshmukh et al., 2012) this will allow for fast disintegration of tablets, however could lead to poor mechanical properties. Therefore, many FDTs are fragile and will break during packing, transport or handling by patients. Many technologies have been used to prepare FDTs, and can be classified into conventional technologies such as freeze drying, tablet molding, direct compression, spray drying and sublimation, or patented technologies (e.g. Zydis, Quicksolv, Flashtab, Orasolv, Wow tab) (Siddiqui et al., 2010). The resultant FDT depends on the technology being used and could therefore have varying properties (Nagar et al., 2011). Some of the patented technologies have disadvantages. For example, Zydis technology (Katou el al., 1993), produced by lypholizing or freeze drying is very light weight and fragile, and must be dispensed in a special blister pack. Similarly Orasolv technology (Wehling et al., 1991) have poor mechanical strength because they are only lightly compressed (Nandy et al., 2011). Other problems that are related to FDTs include hygroscopicity, aqueous solubility, tablet size and drug content (Sharma et al., 2012).

Great efforts have been used to enhance properties of FDTs and adapt the conventional tableting formulation or the process used (Pabari and Ramtoola, 2012) in order to compromise between the two parameters mechanical strength and disintegration time. Kuno et al. (2005) evaluated rapidly

disintegrating tablets manufactured by phase transition of sugar alcohols. However, they reported a 4 time's increase in tablet hardness and an increase in disintegration time after heating and increasing sugar alcohol content. Late and Banga (2009) reported that moisture treatment of FDTs at 85 and 95% increased tablet hardness; however at the same time negatively affected the disintegration time. Zhang et al. (2013) used Eudagrit E-100 to mask the bitter taste of FDT Chinese herbal medicine and found that the hardness of the tablets increased with the increased ratio of Eudragit E-100/drug. However, this lead to a slight increase in disintegration time.

Direct compression represents the simplest and most cost effective tablet manufacturing technique (Arora and Sethi, 2013). The basic principle involves the addition of disintegrants and/or water soluble excipients and/or effervescent agents (Wagh et al., 2010). The choice and role of excipients are important in the formulation of FDTs (Nagar et al., 2011). The addition of superdisintegrants to the formulation plays a major role in the dissolution and disintegration of the tablets, they provide rapid disintegration due to the combined effect of swelling and water absorption by the formulation (Sharma et al., 2012). Superdisintegrants addition technique for preparing FDTs by direct compression has been studied by many researchers and found to be a useful method to provide rapid disintegration (Sharma et al., 2008; Avani et al., 2008; Jain et al., 2009; Bhardwaj et al., 2010; Venkata et al., 2012).

Although the FDTs area has passed its infancy there are still many aspects to improve in the FDTs formulation. The aim of this study was to enhance the properties of FDTs produced by direct compression (using Disintequick MCC-25 in a combination with mannitol which is dissolving quickly) according to a general multilevel factorial design to not only have sufficient hardness to withstand manual handling, but also to have a rapid disintegration time. A progressive two-stage approach was used in this study. Each stage involved the change in the ratio of excipients (Mannitol: Filler) and concentration of superdisintegrant. All FDTs were tested for different parameters such as diameter, hardness, thickness, friability and disintegration time. The identification of interaction between factors, reduction in number of experiments and factual modelling of the data, made general multilevel factorial design a very suitable tool for process optimisation of FDTs.

2. MATERIALS AND METHODS

2.1. Materials

All the excipients used to prepare the tablets were of analytical grade and consisted of: D-mannitol (EC-200-711-8, WGK-2, Sigma-Aldrich, France) used as a diluent; co-processed lactose/ microcrystalline cellulose (MCC) (Distintequik MCC-25, Foremost Farms, USA) as a filler; croscarmellose sodium (CCNa) (CHP Carbohydrate Pirna GmbH + Co. KG, Germany) as a superdisintegrant and magnesium stearate (Pittsburgh, PA, USA) as lubricant.

2.2. Experimental design and validation

A factorial experiment provides a formula for setting up an experiment to test the effects of different factors at the same time (Charles and Carter, 1990). General multilevel factorial design was applied using the statistical software MAT LAB (7.12.09, R2011a) to optimise and evaluate main effects, interaction effects and quadratic effects of each factor (X) on the considered response (Y). This design was selected because it has a certain level of flexibility in choosing the number of levels for each assigned factor. It can be used when the equality of levels may consist constraints towards obtaining more accurate predictable mathematical models. A multilevel factorial design allows for the calculation of coefficients of a second order model (Kuntez and RÖthlisberger, 2002) which is developed based on the regression analysis of the statistically significant variables. The formulation ingredients were the studied independent factors, and included % filler to mannitol (X1) and disintegrant concentration (X2). The dependent variables (responses) were hardness (Y1), tensile strength (Y2) and disintegration time (Y3). For X1, seven levels were assigned as follows; 0, 20, 33.34, 50, 66.67, 80 and 100% w/w, whereas X2 was assigned five levels; 1, 3, 5, 7 and 10% w/w. Therefore, the total prepared formulations were 35. The collected data was randomly split into two parts. The larger part (25 samples) was used for calibration of the polynomial models and the smaller one (10 samples) was used for validation of the built models. The following second order polynomial equation (Eq. 1) was applied as a tool of mathematical modelling (Lewis et al., 1999)

$$Y = b_0 + b_1 X_1 + b_2 X_2 + b_{12} X_1 X_2 + b_{11} X_1^{\,2} + b_{22} X_2^{\,2} \qquad \text{Eq. 1}$$

Where Y is the dependent variable, b0 is the arithmetic mean response of the seven runs, and b1 and b2 are the estimated coefficients of the factors X1 and X2. The main effects X1 and X2 represent the average results of changing one factor at a time from its low to high value.

Three polynomial models were produced and evaluated by plotting the residuals for both data sets (calibration and validation) versus the samples, the predicted responses, the frequency and the probability (not shown). The residuals from a fitted model can be defined as the differences between the observed (true) and predicted responses ($Y_{obs} - Y_{pred}$) (Armstrong, 2006). At each stage, the calculated multiple correlation coefficient (R^2) was shown as an indicator for the model accuracy. Finally, response surface 3D plots and contour plots were generated to allow for graphical illustration of the relationship between the different experimental variables and the responses (Lundstedt et al., 1998).

2.3. Choice of excipients

Croscarmellose sodium (CCNa) was chosen as the superdisintegrant due to its high swelling capacity and effectiveness at low concentrations. Swells 4 – 8 folds in less than 10 seconds (Bala et al., 2012).

Mannitol was chosen as a diluent. However, it could also be regarded as a sweetening agent. It has many physicochemical properties such as its sweet taste, cooling sensation that it leaves in the mouth, hygroscopicity and compactibility (Ohrem et al., 2014). It has also been shown that the use of mannitol in FDTs reduces disintegration time (Mizumoto et al., 2005; Chandraskhar et al., 2009). DisinteQuik MCC25 was chosen as the filler, and is made up of MCC and α-lactose monohydrate. This is a co-processed excipient designed for direct tableting operations where fast disintegration is required. The properties of the two excipients MCC and lactose monohydrate complement each other, and permit the tablets to be made without granulation (Kerry, 2015). Microcrystalline cellulose which makes up 25% of the chosen filler is one of the preferred direct compression binders due to its excellent compactability at low pressures, it is also known to be self-disintegrating (Jivraj et al., 2000; Thoorens et al., 2014). Lactose monohydrate which makes up 75% w/w of the chosen filler, is known to be one of the most common fillers used in tablets, it also has good compactibility properties, has pleasant taste, and is non-hygroscopic (Alderborn, 2013). In a study conducted by Michoel et al. (2002) It was found that co-processed spray dried Microlec 100 composed of 25% w/w microcrystalline cellulose and 75% w/w α – lactose monohydrate showed superior flowability and binding properties compared to physical mixtures of MCC with different lactose grades. Consequently, the combination of CCNa, mannitol and DisinteQuick MCC25 complement one another and impart the desired flowability, compressibility, good mouth feel, and rapid disintegration.

2.4. Formulation of fast disintegrating tablets (FDTs)

FDTs were prepared by direct compression. The formulation (Table 1) consisted of 5 different disintegrant (CCNa) concentrations (1%, 3%, 5%, 7% and 10% w/w). For each concentration seven batches with varying ratios of diluent (D-Mannitol): Filler (Disintequik MCC-25) were used: (1:0), (1:0.25), (1:0.50), (1:1), (0.50:1), (0.25:1), (0:1) w/w, these were expressed as a percentage (% filler to mannitol, Table 1) for ease in data manipulation and interpretation (0, 20, 33.33, 50, 66.67, 80 and 100% w/w). The concentration of lubricant (magnesium stearate) stayed the same in all formulations as 1% (w/w). Tablet excipients were weighed individually on a digital weighing balance (PJ Precisa junior, 400C-3000D, Swis quality, Switzerland) and mixed together in a turbular mixer (WAB Turbula, system Schatz, Willy A. Bacheofen machine, AG Maschinenfabrik, Glen Creston LTD, Switzerland) for 10 minutes at a speed of 20 rpm. Tablets were then compressed at a maintained compression force of 24 psig using a single punch tablet press machine (Manesty machine LTD, type F3, London, UK). Each batch produced consisted of 40 tablets which were flat faced and compressed with a target weight of approximately 300mg.

2.4. Characterisation of FDTs

The formulated FDTs were evaluated for various parameters: diameter, thickness, uniformity of weight, hardness, tensile strength, friability and disintegration time.

2.4.1. Determination of tablet diameter and thickness

The diameter (mm) and thickness (mm) of the tablets were measured using a micrometer screw gauge (Moore and Wright, Sheffield, England) by placing the tablet between two faces (the spindle and anvil face), then turning the ratchet until the sample was trapped between the two faces. Six tablets were taken at random from each formulation (F1 – F7) and the results were calculated as the mean and standard deviation.

Table 1: Composition of the prepared fast disintegrating tablets (FDTs)

Formulation Code	% Filler: Mannitol	Concentration of disintegrant (% w/w)	Amount of Mannitol (mg)	Amount of Filler (mg)	Amount of 1% Disintegrant (mg)	Amount of Lubricant Mg.stearate (mg) 1%	Total tablet weight (mg)
F1	0	1%	294	-	3	3	300
F2	20		235.2	58.8	3	3	300
F3	33.33		196	98	3	3	300
F4	50		147	147	3	3	300
F5	66.67		98	196	3	3	300
F6	80		58.8	235.2	3	3	300
F7	100		-	294	3	3	300
F1	0	3%	288	-	9	3	300
F2	20		230.4	57.6	9	3	300
F3	33.33		192	96	9	3	300
F4	50		144	144	9	3	300
F5	66.67		96	192	9	3	300
F6	80		57.6	230.4	9	3	300
F7	100		-	288	9	3	300
F1	0	5%	282	-	15	3	300
F2	20		225.6	56.4	15	3	300
F3	33.33		188	94	15	3	300
F4	50		141	141	15	3	300
F5	66.67		94	188	15	3	300
F6	80		56.4	225.6	15	3	300
F7	100		-	282	15	3	300
F1	0	7%	276	-	21	3	300
F2	20		220.8	55.2	21	3	300
F3	33.33		184	92	21	3	300
F4	50		138	138	21	3	300
F5	66.67		92	184	21	3	300
F6	80		55.2	220.8	21	3	300
F7	100		-	276	21	3	300
F1	0	10%	267	-	30	3	300
F2	20		214	53	30	3	300
F3	33.33		178	89	30	3	300
F4	50		134	134	30	3	300
F5	66.67		89	178	30	3	300
F6	80		53	214	30	3	300
F7	100		-	267	30	3	300

2.4.2. Uniformity of weight

Twenty tablets from each batch were selected at random and weighed individually on a digital weighing balance (PJ Precisa junior, Swis quality, Switzerland). The average weight of the tablets was then calculated. Percentage deviation of each individual tablet from the average weight was determined.

2.4.3. Mechanical strength

Crushing strength and friability are two important parameters for determining the mechanical strength of tablets (Nagar et al. 2011). The hardness/ crushing strength measured in kg/cm^2 of six tablets taken at random from each batch was determined using a Hardness Tester (SCHIEUNIGE-2E, Model 2E/205, Switzerland). The average hardness ± standard deviation was calculated. The tensile strength, T, for crushing (MPa) was measured using equation (Eq. 2).

$$\boldsymbol{T = 2F / \pi * d * t} \qquad \text{(Eq. 2)}$$

Where F is the crushing load (N), d, the diameter (m) and t, the thickness (m)

2.4.4. Friability test

Friability test was performed on 10 randomly selected tablets using a pre-calibrated friability tester (Model: FRV1000, Copley scientific LTD. Nottingham, England). The drum was rotated at 25 rpm for 4 minutes. The tablets were weighed before and after using the tester and percentage friability was calculated using equation (Eq. 3) (British Pharmacopeia, 2013).

$$\% \boldsymbol{Friability} = \frac{\boldsymbol{w1 - w2}}{\boldsymbol{w1}} \times \boldsymbol{100} \qquad \text{(Eq. 3)}$$

Where, w1= Initial weight before test, w2 = final weight after test

2.4.5. Disintegration test

This method was done following the procedure outlined in the British Pharmacopeia (2013). Six tablets were separately placed into a disintegration test apparatus (Type: NE4-COP, Supplied by Copley scientific, Nottingham, United Kingdom). The basket rack assembly of the apparatus was immersed into 800ml distilled water maintained at 37 ± 2^{o}C. The time (seconds, s) was recorded when the tablet had fully disintegrated and no residue was remaining. The results were recorded as the mean ± standard deviation.

2.5. Statistical analysis

Results obtained from the experiments were expressed as a mean ± standard deviation using Microsoft Excel software (Redmond, WA, USA). Statistical experimental design, evaluation of the models quality

of fit and analysis of the data, including calculation of the constants and regression coefficients was conducted using the statistical software MAT LAB (7.12.09, R2011a) MathWorks, USA.

3. RESULTS AND DISCUSSION

The results obtained from characterisation of tablets are summarised in Tables (2 & 3) and Figure 1. All FDT formulations showed acceptable uniformity of weight (Table 2) since they complied with the British Pharmacopeia standards (2013). Which states that for an average tablet weight of 250mg or more, not more than two tablets should differ from the mean by more than 5%. When preparing directly compressed tablets, the compression mix has to flow to ensure consistent tablet weight (Thoorens et al., 2014). Slight variation seen in tablet weight could be attributed to differences in bulk density of the formulation (Late el al., 2009). Another reason could be due to the presence of high concentrations of mannitol in some of the formulations (F1 – F3). Lieberman et al (1964) describes mannitol in pharmaceutical formulations as hindering the free flow into the tablet dies.

Tablet diameter showed very low variability, tablet thickness also showed low variability (Table 2) in most of the formulations, this supports the reproducibility of the formulation and tableting process used for this study. Tablets' diameter and thickness results were used for calculating tablets' tensile strength

Table 2: Characteristics of fast disintegrating tablets (weight, thickness and diameter)

Weight (mg)					
Formulation Code	**1%**	**3%**	**5%**	**7%**	**10%**
F1	247.2 ± 13.92	253.2±25.02	301.4±27.50	274.5±17.1	285.1±23.2
F2	255.5 ± 15.43	280.2±16.83	305.3±17.10	291.8±17.5	269.2±26.0
F3	279.7 ± 23.69	304.7±16.41	304.7± 9.14	300.9±12.0	294.5±13.5
F4	308.7 ± 5.98	307.3±9.39	304.5± 8.20	297.4±9.6	308.5±14.4
F5	305.9 ± 5.93	314.6±16.18	300.8± 6.66	303.4±11.1	307.3±10.8
F6	302.9 ± 6.03	316.1±9.97	294.5±12.06	301.1±16.7	307.5±14.4
F7	305.1 ± 6.82	322.5±12.96	291.6±12.36	308.1±9.1	305.4±14.0
Thickness (mm)					
F1	2.73 ± 0.221	2.96±0.202	3.35±0.189	3.16±0.13	3.14±0.18
F2	2.82 ± 0.352	3.10±0.346	3.33±0.188	3.21±0.18	3.08±0.27
F3	2.95 ± 0.081	3.09±0.017	3.19±0.171	3.11±0.14	3.11±0.19
F4	2.96 ± 0.055	3.02±0.054	3.30±0.202	3.32±0.22	3.03±0.06
F5	2.95 ± 0.041	3.24±0.225	3.48±0.014	3.09±0.17	3.36±0.18
F6	3.43 ± 0.016	3.39±0.176	3.27±0.188	3.27±0.20	3.20±0.28
F7	3.33 ± 0.228	3.12±0.289	3.24±0.292	3.19±0.26	3.22±0.27
Diameter (mm)					
F1	9.57 ± 0.008	9.57 ± 0.004	9.59±0.004	9.58±0.00	9.58±0.01
F2	9.57 ± 0.017	9.58 ± 0.005	9.59±0.004	9.58±0.00	9.59±0.01
F3	9.59 ± 0.005	9.58 ± 0.004	9.59±0.008	9.58±0.01	9.58±0.00
F4	9.58 ± 0.008	9.58 ± 0.006	9.58±0.006	9.58±0.00	9.59±0.01
F5	9.58 ± 0.005	9.57 ± 0.000	9.58±0.004	9.57±0.00	9.59±0.00
F6	9.58 ± 0.005	9.58 ± 0.004	9.58±0.000	9.57±0.00	9.58±0.00
F7	9.57 ± 0.004	9.58 ± 0.005	9.57±0.000	9.56±0.00	9.57±0.00

Weight (n = 20), thickness and diameter (n = 6)

Table 3: Characteristics of fast disintegrating tablets (mechanical strength and friability)

Hardness (N)					
Formulation Code	**1%**	**3%**	**5%**	**7%**	**10%**
F1	38.71 ± 4.33	16.76 ± 4.26	38.87±8.89	42.47±5.60	35.61±6.46
F2	67.86 ± 8.09	60.76 ± 13.63	66.56±3.79	55.45±8.02	53.87±6.61
F3	93.92 ± 2.27	89.67 ± 4.75	88.85±6.67	73.86±5.04	72.68±4.04
F4	132.46 ± 8.35	110.58 ± 4.27	122.01±6.06	96.53±4.00	95.55±8.54
F5	177.87 ± 7.78	174.77 ± 11.03	165.95±4.71	137.69±5.57	150.27±9.14
F6	198.39 ± 0.00	193.39 ± 3.26	192.41±4.67	161.86±18.11	184.08±7.45
F7	379.36 ± 0.00	164.23 ± 21.99	380.32 ±0.00	415.85 ±0.00	254.31±0.00
Tensile Strength (MPa)					
F1	0.95 ± 0.124	0.38 ± 0.094	0.77±0.177	0.90±0.15	0.75±0.13
F2	1.61 ± 0.128	1.32 ± 0.351	1.33±0.129	1.15±0.12	1.17±0.21
F3	2.11 ± 0.086	1.93 ± 0.099	1.86±0.190	1.58±0.07	1.56±0.11
F4	2.97 ± 0.196	2.44 ± 0.074	2.47±0.222	1.94±0.19	2.09±0.17
F5	4.01 ± 0.147	3.61 ± 0.406	3.17±0.082	2.97±0.19	2.98±0.29
F6	3.84 ± 0.018	3.81 ± 0.245	3.92±0.233	3.31±0.50	3.85±0.32
F7	4.82 ± 0.369	4.90 ± 0.398	4.71±0.451	3.88±0.32	5.29±0.44
Friability (%)					
F1	16.91	39.562	15.979	11.59	12.35
F2	13.09	3.845	2.217	3.18	2.74
F3	0.987	0.970	10.836	1.44	1.15
F4	6.483	6.481	5.652	7.33	8.41
F5	0.328	0.444	0.433	0.46	0.49
F6	0.198	0.257	3.051	0.30	0.41
F7	0.097	0.030	0.101	0.00	0.19

Hardness and tensile strength (n = 6), friability (n = 10)

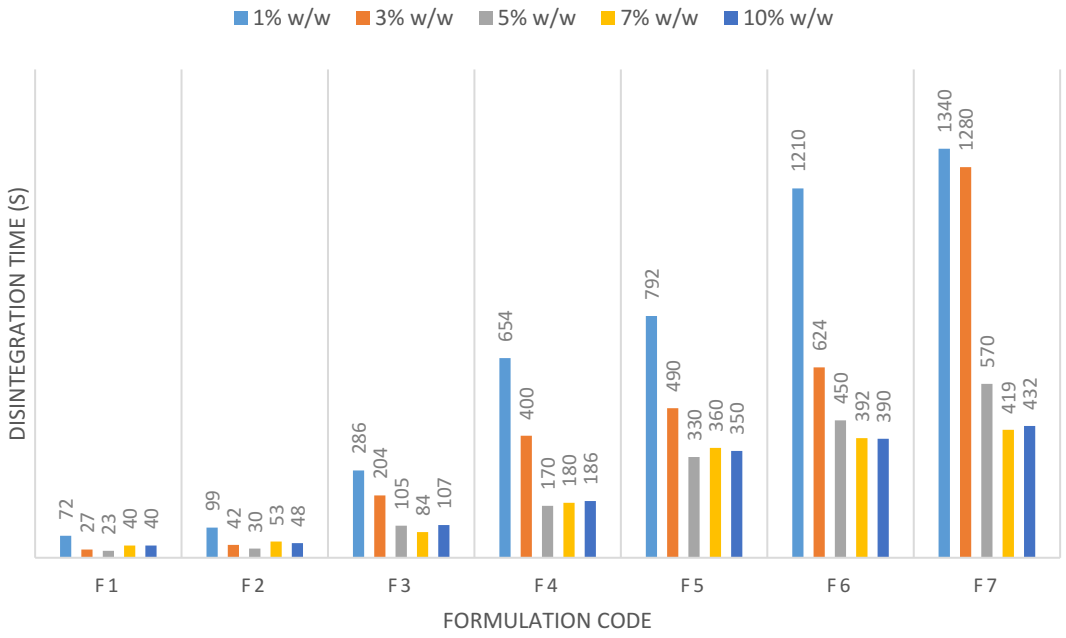

Figure 1. Disintegration time (seconds) of all FDT formulations F1 – F7 at varying disintegrant concentrations (1% - 10%); for formulation composition refer to Table 1.

3.1 General multilevel factorial design - Statistical analysis and mathematical modelling

The data presented (Table 3 and Fig. 1) summarise the responses for Y1 (hardness), Y2 (tensile strength) and Y3 (disintegration time) of FDTs. These values were analysed using statistical software MAT LAB. The polynomial relationships generated for each response variable using multiple regression analysis are expressed in equations 4 – 6. The model of best fit was determined by comparing the statistical parameters correlation coefficient (R^2) and the confidence intervals (P). Results of model summary statistics are presented in Table 4.

$$Y1\ (Hardness,\ N) = 86.2473 - 0.8024 \times X1 - 9.2657 \times X2 + 0.1566 \times X1.X2 + 0.0263 \times X1^2 + 0.1741 \times X2^2 \quad (Eq.\ 4)$$

$$Y2\ (Tensile\ Strength,\ MPa) = 0.7869 + 0.0412 \times X1 - 0.0515 \times X2 \quad (Eq.\ 5)$$

$$Y3\ (DT,\ s) = 96.8845 + 10.7433 \times X1 - 83.6369 \times X2 - 1.3071 \times X1.X2 + 0.0445 \times X1^2 + 9.1552\ X2^2 \quad (Eq.\ 6)$$

Table 4. Model summary statistics

Responses (Y)	R^2	Predicted R^2	P
Hardness (Y1)	0.8413	0.8350	<0.0001
Tensile Strength (Y2)	0.9457	0.9611	<0.0001
Disintigration Time (Y3)	0.9054	0.9592	<0.0001

The polynomial equations (Eq. 4-6) above indicate the effect of independent factors % filler to mannitol (X1), disintegrant concentration (X2) and their interactions on the responses Y1, Y2 and Y3. Coefficients containing both factors (e.g. X1X2) shows the changes in response when two factors are simultaneously changed (Pathan et al., 2013), while factors at higher order (Xn^2) represents the quadratic relationships (i.e. non-linearity) (Pabari and Ramtoola, 2012; Zhang et al., 2013).

It can be observed that R^2 is reasonably high for all responses (Table 4), this indicates a high degree of correlation between the experimental and predicted responses. The R^2 of 0.8413 for hardness indicates that over 84.13% of the variation in the response is accounted for in the regression equation, similarly over 94.57% for tensile strength and over 90.54% for disintegration time. Only statistically significant coefficients ($P < 0.05$) were kept in the equation. Analysis of variance (ANOVA) of the responses demonstrates that the quadratic model was significant ($P < 0.0001$) and valid for each of the responses (Table 4).

The sign and magnitude of the main effects signify the relative influence of each factor on the response (Dhiman and Singh, 2012). The data clearly indicates that the dependent variables hardness, tensile strength and DT are strongly dependent on the selected independent variables (X1 and X2). In equationS (5) and (6), the positive regression coefficient of variable X1 suggests, as would be expected, an increase in tensile strength and disintegration time with an increase in % filler to mannitol. However, the negative regression coefficient seen for independent factor (X2) in equations (4-6) indicates a decrease in hardness, tensile strength and disintegration time with an increase in disintegrant concentration. The interaction of % filler to mannitol (X1) and disintegrant concentration (X2) had a desirable positive impact on hardness (i.e. causing an increase in hardness), on the other hand they had a desirable negative impact on disintegration time (i.e. reducing DT).

3.2. Analysis of data

The 3 – dimensional response surface plots and contour plots for the effect of % filler to mannitol (X1) and disintegrant concentration (X2) on FDT hardness (Y1), tensile strength (Y2) and disintegration time (Y3) are shown in figures 2 – 4. Response surface plots allow for visual observation of the significance

of regression equations by graphically depicting maxima and minima (Late and Banga, 2010). The variation in values is demonstrated by different colour regions.

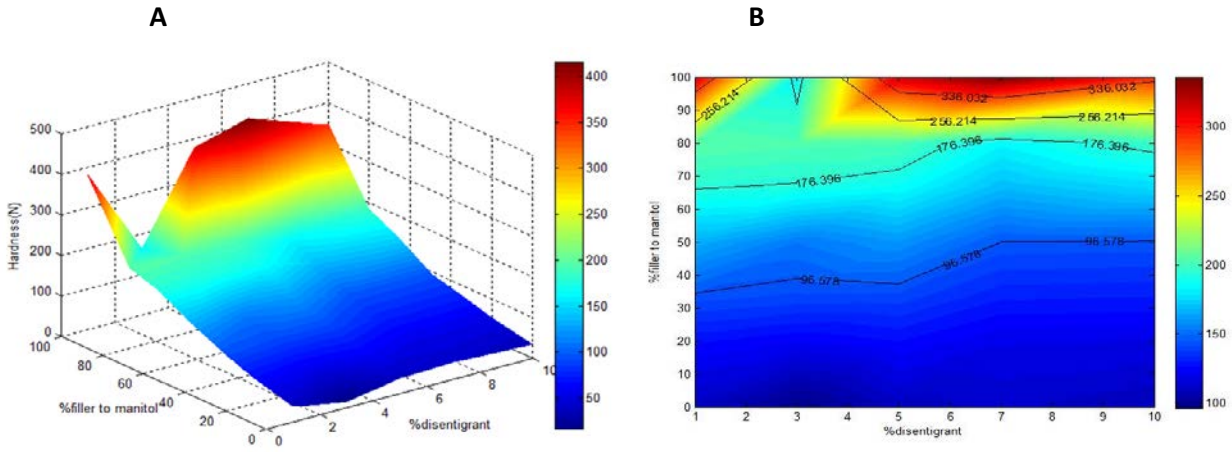

Figure 2. Response surface (A) and Contour plot (B) showing the effect of % filler to mannitol (X1) and disintegrant concentration (X2) on Hardness (Y1)

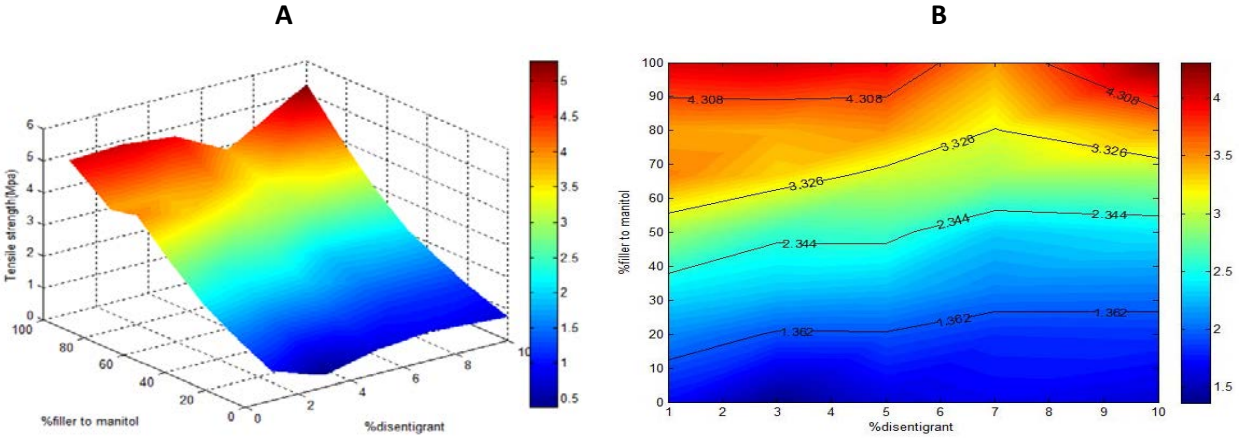

Figure 3. Response surface (A) and Contour plot (B) showing the effect of % filler to mannitol (X1) and disintegrant concentration (X2) on tensile strength (Y2)

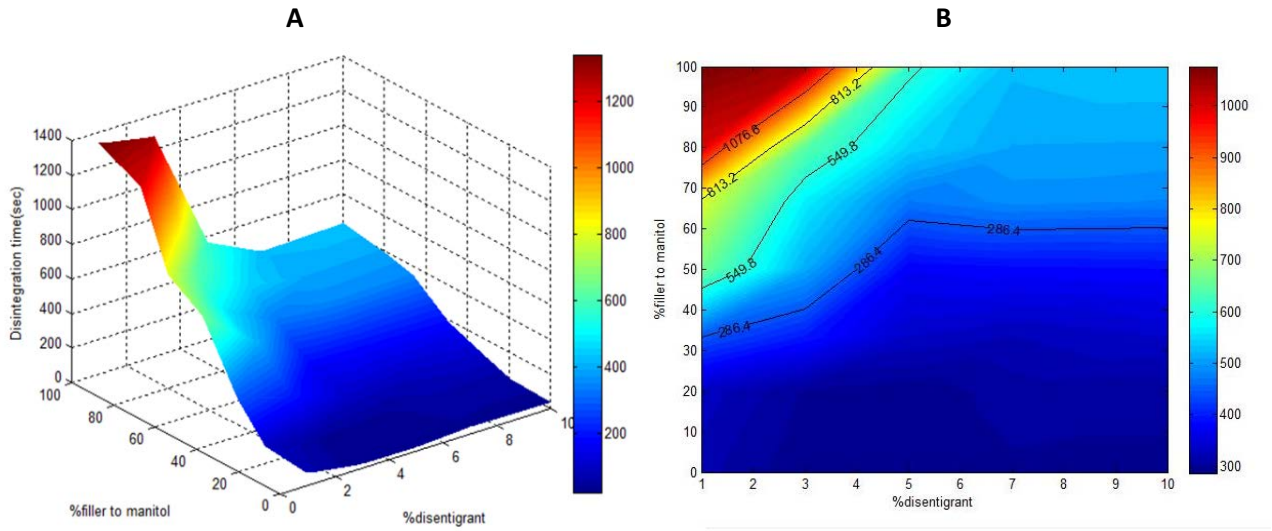

Figure 4. Response surface (A) and Contour plot (B) showing the effect of % filler to mannitol (X1) and disintegrant concentration (X2) on disintegration time (Y3)

3.2.1. Hardness of tablets (Y1)

The hardness of a tablet is an indication of its strength, it is defined as the force applied across its diameter in order to break the tablet. Tablets should be able to resist chipping, abrasion or breaking under conditions of storage, transformation or handling (Saroha et al., 2013; Nagar et al., 2011) but they should also have no problem in disintegrating or dissolving (Lee, 2008). Generally, from the results it was evident that the hardness of all tablets appeared higher in the presence of larger concentrations of the filler. From the response surface plot (Fig. 2) it was found that an increase in X1 (% filler to mannitol) from 0% to 20% lead to a sharp increase in Y1 (hardness) from 38.71N to 67.78N at low level of disintegrant concentration (X2). Increasing X1 further to 100% lead to a further increase in hardness to 379.36 N (9.8 fold increase). At higher concentrations of X2 (10%) the trend seen was similar showing a sharp increase (7.1 fold) from 35.61 N to 254.31 N as X1 increased from 0% - 100% w/w.

On the other hand, it was found that an increase in disintegrant concentration lead to small decreases in hardness. it was found that an increase in X2 (disintegrant concentration) from 1% to 10% lead to a slight decrease in Y1 (hardness) from 38.7N to 35.61N at low level of X1 (% filler to mannitol). The results were similar at all concentrations of X1 showing a small decrease in hardness. At 80% and 100% of X1 (% filler to mannitol) the results showed a general very small decrease in hardness from 198.39N to 184.08 N and from 379.36 N to 254.31 N with an increase in X2 from 1% to 10%.

In the case of this experiment X1 shows more impact on hardness of FDTs than X2. The positive effect of X1 was a determinant factor of Y1; this made it possible to achieve tablets with adequate mechanical strength under minimum pressure.

Another tablet property related to crushing strength is friability. The idea behind friability tests is to mimic the kind of forces that tablets are subjected to during handling between its production and administration, and to determine the ability of the tablet to withstand abrasion during those conditions. (Odeniyi et al., 2003; Alderborn, 2013). In some of the formulations with the absence of filler, lamination or capping was observed. Generally, formulations containing larger amounts of filler passed the BP limit test where friability should be < 1%. For these tablets there were no signs of cracking, splitting or breaking. At 1% and 3% w/w disintegrant concentration both F1 and F2 showed high friable tablets with % powder loss between 3.8- 39.5% (Table 3); at 5% w/w disintegrant, F2 showed only 2.2% powder loss and at 7% and 10% w/w disintegrant, F1 with 100% mannitol showed high value of friability (~12%), while the friability values were greatly reduced to about 3% for F2 (i.e. with 80% mannitol+20% Distintequik MCC-25) and to nearly 1% for F3 (i.e. with 66.67% mannitol+33.33% Distintequik MCC-25). Microcrystalline cellulose, MCC, is known to improve the compactibility/ tableting, and is one of the preferred direct compression binders (carlin, 2008; Thoorens et al., 2014).

Belda and Mielck (1996) found that cellactose, which is a co-processed compound consisting of 25% cellulose and 75% α-lactose monohydrate exhibited enhanced crushing strength compared to powder mixtures of the same concentration. Reimerdes and Aufmuth (1992) reported that cellactose was found to impart a significant increase in crushing strength of tablets and reduced disintegration time, when compared with dry blends. It has also been reported that the good compactibility of tablets containing cellactose could be attributed to the synergetic effect of consolidation by fragmentation of lactose and plastic deformation of cellulose (Gohel, 2005; Arida, 2008). This would explain why formulations with small amounts of co-processed Distintequik MCC-25 with mannitol FDTs can enhance mechanical strength properties of tablets with keeping fast disintegrating time; those properties are very desirable/demanding for FDTs. Hence and according to this study, F2 (with 80% mannitol+20% Distintequik MCC-25+5% w/w croscarmellose sodium) and F3 (with 66.67% mannitol+33.33% Distintequik MCC-25+7% or 10% w/w croscarmellose sodium) can overcome the issues (for example processing technique, using blister packs and hygroscopicity) with the most of existing commercially available FDTs.

3.2.2. Tensile strength of tablets (Y2)

Response surface plot (Fig. 3) described the effects of X1 (% filler to mannitol), X2 (disintegrant concetration) and their interactions on Y2 (tensile strength). The observations seen were similar to that described for hardness. It was found that Y2 (tensile strength) was strongly effected by X1 (% filler to mannitol), with a sharp increase in Y2 (tensile strength) from 0.95 MPa to 4.82 MPa as X1 (%

filler/Mannitol) increased from 0% to 20% at low level X2 (disintegrant concentration). This trend was repeated at higher concentrations of X2, with an increase in Y2 from 0.77 MPa to 4.71 MPa at 5% X2, and from 0.75 MPa to 5.29 MPa at 10% X2. The positive effect of X1 as seen in regression equation 3 and response surface plot was a determinant factor of Y2, this made it possible to achieve tablets with adequate tensile strength.

The effect of disintegrant concentration on Y2 (tensile strength) was small, with a small decrease in Y2 from 0.95M to 0.75M as X2 (disintegrant concentration) increased from 1% to 10% at low level of X1 (% filler to mannitol). This pattern was repeated at higher concentrations of X1. However, at 80% and 100% X1, the decrease in tensile strength was even smaller and the results were not systematic in one direction (see also Table 3).

3.2.3. Disintegration time (DT) of tablets (Y3)

Superdisintegrants accelerate disintegration of tablets by virtue of their ability to absorb a large amount of water when exposed to an aqueous environment. The combined effect of swelling and water absorption results in breaking of tablets and therefore faster disintegration (Sharma et al., 2012; Vimal et al., 2013). Combinations of swelling and/or wicking and/or deformation are the mechanisms of disintegrant action. The disintegrants have the ability to oppose the efficiency of the tablet binder and the physical forces that act under compression to form the tablet (Vimal et al., 2013). According to the BP (2013), orodisoersible tablets disintegrate within 3 minutes. For formualtions F1 and F2, tablets disintegrated at all disintegrant concentrations in less than 3 minutes (Fig. 1). The fastest disintegration time of 23 seconds being for F1 containing 5% disintegrant and 0% filler to mannitol.

Response surface plot (Fig. 4) described the effect of X1 (% filler to mannitol) and X2 (disintegrant concentration) and their interaction on Y3 (DT). It was found that DT was strongly affected by X1 and X2.

Response surface plot shows that DT (Y3) was directly proportional to % filler/mannitol (X1) with a rapid and sharp increase in DT as X1 increased from 0% to 100% at low disintegrant concentrations (X2). The trend was repeated at high level of X2 with a sharp increase in Y3 from 40 s to 432 s as X1 increased from 0% to 100%. It is clear from the response surface plot and from Fig 1. that the lowest disintegration times were achieved at 5%, 7% and 10% disintegrant concentrations and in formulations containing no or only small amounts of filler. The results also show that Y3 was inversely proportional to X2 showing a sharp decrease in DT from 72 seconds to 40 seconds as disintegrant concentration increased from 1% to 10% at 0% X1 (% filler to mannitol). The trend was repeated with the rise in X1 showing a sharp decrease in DT from 99 s to 48 s at 20% filler to mannitol and from 1340 s to 432 at

100% filler to mannitol as disintegrant concentration increased from 1% to 10%. Therefore it is clear that DT (Y3) is greater at higher levels of % filler to mannitol (X2). This observation could be attributed to the increase in hardness observed (Fig.2, Table 3) with an increase in % filler to mannitol. Similar observations were found in a study by Marais et al (2003) where the disintegration time of DC furosemide tablets decreased as the disintegration concentration (croscarmellose sodium A) increased above 0.625% w/w. However, an increase in the crushing strength as a result of increased compression force prolonged the disintegration time. The increased hardness was thought to lead to reduced penetration of liquid into the tablet structure hence reducing the disintegrating force inside the tablet. In this current study, there was a clear increase in tablet hardness with the increase in % filler to mannitol.

Formulations F1, despite they showed very fast disintegration properties, which is expecting as they contain 100% mannitol, they had poor mechanical properties. Generally, most of tablets in formulations F2 and F3 had sufficient hardness, hardness values ranged between 53.87 N – 89.67 N (5.49 kgf – 9.15 kgf), and at the same time disintegrated at about or less than 3 minutes; the tablets with the maximum hardness i.e. 89.67 N disintegrated within 204 seconds and was for F3 with 3% disintegrant and 33.33% filler to mannitol; and the F2 formulation containing 5% disintegrant and 20% filler to mannitol had a hardness of 66.56 N (6.79 kgf), a tensile strength of 1.33 MPa and disintegrated within 30 seconds (the fastest disintegration time for F2-F3). Formulations F4 – F7 had hardness values ranging between 95.55 N (9.74 kgf) and 415.85 N (42.4 kgf), these formulations as would be expected produced considerably higher disintegration times (Fig. 1)and would therefore not be suitable as FDTs.

4. CONCLUSION

Fast disintegrating tablets have become a rapid growing area in the pharmaceutical industry. Two of the key parameters for producing desirable and successful FDTs is rapid disintegration upon placing in the mouth, and good mechanical strength to withstand handling, packaging and transport. This study demonstrated that the FDTs prepared by direct compression, were successfully optimised by applying general multilevel factorial design. Disintegrant concentration and % filler to mannitol were observed to have an interactive effect on the hardness, tensile strength and disintegration time of the FDTs. The mathematical models showed a good degree of correlation between experimental and predicated responses of the optimised formulations. The optimum formulation regarding DT was found to be for F2 with 5% disintegrant and 20% filler/mannitol. This formulation gave the best results with fast disintegration (30 seconds) and strong mechanical properties showing a hardness of 66.56 N (6.79 kg/cm^2) and tensile strength of 1.33 MPa. These process parameters may have wider applications within the pharmaceutical industry, saving both time and cost of the formulation.

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