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Original Research Article

Development and optimization of fluoxetine orally disintegrating tablets using Box-Behnken design

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Abstract

Purpose: *To develop and optimise some variables that influence fluoxetine orally disintegrating tablets (ODTs) formulation.*
Methods: *Fluoxetine ODTs tablets were prepared using direct compression method. Three-factor, 3-level Box-Behnken design was used to optimize and develop fluoxetine ODT formulation. The design suggested 15 formulations of different lubricant concentration (X_1), lubricant mixing time (X_2), and compression force (X_3) and then their effect was monitored on tablet weight (Y_1), thickness (Y_2), hardness (Y_3), % friability (Y_4), and disintegration time (Y_5).*
Results: *All powder blends showed acceptable flow properties, ranging from good to excellent. The disintegration time (Y_5) was affected directly by lubricant concentration (X_1). Lubricant mixing time (X_2) had a direct effect on tablet thickness (Y_2) and hardness (Y_3), while compression force (X_3) had a direct impact on tablet hardness (Y_3), % friability (Y_4) and disintegration time (Y_5). Accordingly, Box-Behnken design suggested an optimized formula of 0.86 mg (X_1), 15.3 min (X_2), and 10.6 KN (X_3). Finally, the prediction error percentage responses of Y_1, Y_2, Y_3, Y_4, and Y_5 were 0.31, 0.52, 2.13, 3.92 and 3.75 %, respectively. Formula 4 and 8 achieved 90 % of drug release within the first 5 min of dissolution test.*
Conclusion: *Fluoxetine ODT formulation has been developed and optimized successfully using Box-Behnken design and has also been manufactured efficiently using direct compression technique.*

Keywords: *Box-Behnken experimental design, Orally disintegrating tablets, Direct compression, Antidepressant, Magnesium stearate, Mixing time*

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INTRODUCTION

Up to one-third of people in all age groups have experienced swallowing issues during their lifetime [1]. The increased prevalence of swallowing issues and the development of clinically significant dysphasia (difficulty in swallowing) can be observed with increasing age, intensity of care required, and the number of diseases as well as diseases with dysphasia inducing co-morbidity [2]. ODTs greatly improve patients' compliance as it is easily taken without the need of water. It provides very rapid onset of action for patients in which it promote pregastric

absorption of the drug molecules through buccal, sublingual, oropharyngeal, and esophageal membranes. Moreover, it avoids the first-pass hepatic metabolism leads to elevate bioavailability and reduces drug side effects [3].

Some manufacturing technologies of ODTs include direct compression, wet granulation, and lyophilization [3]. The direct compression method is the easiest and cost-effective method for the production of ODTs [4,5]. Lubrication is a critical element in tablet formulation. Lubricants are used to diminish the friction and adhesion of the powder blend to the punches and die wall [6]. Magnesium stearate is considered as the most common, chemically stable, and metallic salt boundary lubricant with high melting point, but it is hydrophobic [7]. Hence, lubricant concentration has been reported as one of the independent variables for experimental design [5,8,9]. In ODTs, it is important to keep quick disintegration properties of the tablets with adequate hardness [10]. Thus, optimizing the amount of magnesium stearate and mixing time is critical in the manufacturing of ODTs [5].

Optimization is a procedure that exploits available resources to obtain the best possible results. The manner of try and error that was extensively used before is now switched by the optimization system that finds a wide range of application in chemistry and pharmaceutical industry in the meantime [11]. Response surface methodology (RSM) is an assembly of mathematics and statistics procedures that is quite beneficial for the analysis and modelling of problems in which the optimized response of interest is influenced by numerous variables and objectives [12]. Box-Behnken experimental design offers 3 levels for each factor and involves a particular subsection of factorial blends from the 3k factorial design [12,13].

Optimization techniques have been employed by several researchers in the design and development of ODTs [14, 15]. However, some researchers had developed and prepared fluoxetine HCl in ODTs formulation using try and error methodology and they also used either wet granulation or sublimation techniques in order to manufacture the fluoxetine ODTs [16–18]. Consequently, this Box-Behnken experimental design will be the technique of choice to develop and optimize the fluoxetine ODTs. The design helps to develop the work methodology of fluoxetine ODTs. The design can minimize the number of trials, time, money, and gives developed formulation.

The World Health Organization has listed fluoxetine as an essential medicine [19]. Fluoxetine is a selective serotonin reuptake inhibitor indicated in the treatment of major paediatric depression, adults and children obsessive compulsion disorder, panic, premenstrual dysphoric disease, autism in adult, and trichotillomania [20,21]. The bioavailability of fluoxetine after oral administration has been reported to be up to 72 %, and the elimination of half-life ranged between 1 to 4 days [22]. Fluoxetine HCl is nominated for this work because it is widely used as antidepressant drug. In the present study, direct compression technique was used to prepare fluoxetine ODTs and Box-Behnken experimental design employed to optimize the variables, including lubricant concentration, mixing time, and compression force through investigating their impact on the tablet weight, thickness, hardness, friability (%), and disintegration time. Moreover, the drug release profile is monitored as well.

EXPERIMENTAL

Materials

The following chemicals were obtained and used as received. Fluoxetine HCl was purchased from Xi'an Realin Biotechnology Co., Xi'an, China. Microcrystalline cellulose was purchased from JRS Pharma, Aalen, Germany. Lactose spray dried 250 was purchased from DFE pharma, Borculo, Netherland. Croscarmellose sodium was purchased from FMC Biopolymer, Philadelphia, USA. Magnesium stearate was purchased from Fisher Scientific, Pittsburgh, PA, USA. All chemicals and reagents used were of analytical grade.

Flow properties of the powder blend

It is very important to maintain an excellent flowability property of the powder blends to keep the filling of the punches spaces with the required amount of powder during the process of tablet compression. Therefore, after weighting and mixing the powders together before the tablet compression process took place the powder flowability should be monitored. Hausner ratio, Carr's index, and angle of repose were used to evaluate the flow properties of powders. Hausner ratio and Carr's index were evaluatedby monitoring both bulk and tapped volume of the powder [23,24]. Bulk density (dB) of the designed powder formulation was calculated according to the method of Martin *et al* [25], while tapped density (dT) was determined according to Carr

[23] and Sheehan [24]. Powder flowability properties were determined using Eqs 1 and 2.

Carr's index = 100(dT – dB)/dT ……. (1)

Hausner ratio = dB/dT …….. (2)

Angle of repose was calculated using Eq 3 [24,25].

Tan (α) = height/0.5 base …… (3)

All measurements were carried out in triplicate and mean ± standard deviation (SD) computed.

Box–Behnken experimental design

Box–Behnken experimental design (33) of the statistical package, Statgraphics® Centurion XV, version 15.2.05 (Statpoint Technologies Inc, Warrenton, Virginia, USA), was used to assess the effects of selected independent variables on the variables responses to optimize the ODTs formulation procedure. This strategy is used to optimize the procedure using a lesser number of experimental trials by investigating quadratic response surfaces; and for the creation of second order polynomial models. The levels of factor were coded as low, medium, and high settings (−1, 0, and +1) [12,26].

Preliminary experiments revealed that the chosen independent and dependent variables along with their levels and constraints as shown in Table 1 had a significant effect on the ODTs formulation. The chosen independent variables were the percentage of lubricant concentration (X_1), mixing time (X_2), and compression force (X_3). The observed responses of the dependent variables were the tablets weight (Y_1), thickness (Y_2), hardness (Y_3), % friability (Y_4), and *in-vitro* disintegration time (Y_5). A total of 15 experimental formulae were planned by Box-Behnken design (Table 2).

A (3^3) Box-Behnken design was employed in this work and extended to optimize the fluoxetine ODTs formulation. Through generating the polynomial equations concerning the dependent and independent variables, the procedure optimized the values of X_1, X_2, and X_3, which gave the best wanted possible values of Y_1, Y_2, Y_3, and Y_4 under controlled circumstances. A new formulation was prepared according to the predicted levels of X_1, X_2, and X_3. Subsequently, the observed responses (Y_1, Y_2, Y_3, Y_4, and Y_5) matched the predicted data and the residual, as well as the residual errors (%) were then calculated.

Preparation of fluoxetine HCL orally disintegrating tablets

Tablets (300 mg) containing fluoxetine HCl were manufactured by direct compression method under standardized conditions, according to the formulation specified in the Box–Behnken design (Table 2). Each formulation consisted of fluoxetine HCl (6.67 %), microcrystalline cellulose (30 %), croscarmellose sodium (4 %), and spray dried lactose (to 100 %) and were then mixed together for 15 min. Finally, magnesium stearate (0.5, 1 or 1.5 %) was added and mixed for 2, 13.5 and 25 min. After that 100 g from each formulations powder blends were subjected to the flowability test. Additionally, the remaining formulations powder blends were pressed at 5, 10 and 15 KN using the rotary tablet press (RoTab T, KG Pharma, Berlin, Germany).

Table 1: Independent factors with their levels and dependent variables with their constraints investigated by Box-Behnken design

Variable	Code	Units	Level			Continuous
			Low (–1)	***Medium** (0)*	***High (***1)	
Independent						
Lubricant concentration	X_1	*%*	0.5	1	1.5	Yes
Mixing time	X_2	*min*	2	13.5	25	Yes
Compression force	X_3	*KN*	5	10	15	Yes
Dependent	**Code**	***Units***	***Constraints (%)***			***Research goal***
			Low	***High***		
Weight	Y_1	*mg*	299.1	319.2		300 ±7.5%
Thickness	Y_2	*mm*	4.2	4.72		Minimize
Hardness	Y_3	*Kp*	1.2	8.2		Maximize
Friability	Y_4	*%*	0.06	2.5		Minimize
Disintegration time	Y_5	*sec*	11.42	45.45		Minimize

Table 2: Independent variables and dependent responses employed with each designed formula

Formula code	Independent variable			Dependent variable				
	X_1	X_2	X_3	Y_1	Y_2	Y_3	Y_4	Y_5
F1	1.0	25.0	15.0	315.5	4.22	6.3	0.09	31.01
F2	1.5	2.0	10.0	303.3	4.22	5.1	0.33	25.97
F3	1.0	25.0	5.0	312.1	4.65	1.3	2.14	12.42
F4	1.0	2.0	5.0	300.9	4.55	1.8	1.13	11.42
F5	1.5	13.5	5.0	319.2	4.73	1.4	1.96	12.53
F6	1.5	25.0	10.0	313.5	4.3	4.5	0.38	25.68
F7	0.5	2.0	10.0	299.1	4.24	5.3	0.32	20.07
F8	0.5	13.5	5.0	312.3	4.76	1.2	2.5	11.89
F9	1.0	2.0	15.0	300.2	4.08	8.2	0.06	40.88
F10	1.5	13.5	15.0	311.5	4.18	6.6	0.16	45.45
F11	0.5	13.5	15.0	311.1	4.2	7.3	0.16	27.98
F12	0.5	25.0	10.0	313.6	4.37	4.5	0.32	19.13
F13	1.0	13.5	10.0	308.3	4.29	4.4	0.19	22.29
F14	1.0	13.5	10.0	307.5	4.27	4.3	0.2	22.02
F15	1.0	13.5	10.0	309.2	4.31	4.5	0.18	22.78

Evaluation of ODT thickness, weight variation and hardness

The thickness (mm), uniformity of weight and hardness (20 tablets) were determined using ERWEKA Multi-Check 5.1 (ERWEKA GmbH, Heusensatamm, Germany).

Tablet friability test

Tablet friability (%) was determined using ERWEKA, TA3R friabilator (ERWEKA GmbH, Heusensatamm, Germany). it rotated for 4 min at 25 rpm.

Drug content determination

Drug content (10 Tablets) was determined according to the USP requirements. Tablets were weighed separately, crushed, and the drug was extracted with 0.1 N hydrochloric acid, filtered, and the content (%) determined by Shimadzu UV-1700 spectrophotometer (Shimadzu Corporation, Kyoto, Japan) at a wavelength of 225 nm after suitable dilution [3,16].

Assessment of *in vitro* disintegration time

The test was carried out in distilled water according to the USP30-NF25 requirements using a disintegration tester (ERWEKA GmbH, Heusensatamm, Germany). The apparatus was maintained at 37 ± 2 °C [27], and the time taken for the ODT to pass through the screen or till no solid residue remains on the screen was recorded as the disintegration time.

In vitro dissolution study

In vitro dissolution was carried out according to the USP30-NF25, using an automated dissolution tester (ERWEKA, Germany) attached to an automated sampler (SP-100 peristaltic pump, Somerset, NJ, USA). Dissolution was done in 900 mL phosphate buffer at pH of 6.8 ± 0.05 and 37 ± 0.5 °C temperature to simulate saliva fluid. The paddle rotated at 50 rpm. The samples were withdrawn automatically after 1, 2, 3, 4, 5, 10, and 15 min and were analyzed at a wavelength of 225 nm [28].

RESULTS

The designed fluoxetine ODTs formulations powder blends were subjected to flowability property testing, before their compression into ODTs through measuring the Hausner ratio, Carr's index, and angle of repose as displayed in Table 3. The 15 formulations powder blends displayed a flowability properties ranged from good to excellent as seen in Table 3.

ODT weight, as seen in Table 2, ranged between 299.1–319.2 mg with F5 and F7 respectively. All prepared ODTs were around 300 mg ± 7.5 %. Accordingly, all the ODT formulations met the United States pharmacopoeia requirements concerning the homogeneity of weight.

The Pareto chart (Figure 1) showed that variable X_2 only extended after the reference line and the relatively larger coefficient for these terms is shown in the regression equation (Eq 4).

Therefore, only the lubricant mixing time (X_2) had a significant effect on the tablet weight variation (Y_1) with a positive coefficient. So, X_2 displayed a direct proportional effect on Y_1 for all formulations, although the ODT still within the USP requirements (±7.5 %). Meanwhile X_1 and X_3 had an insignificant effect on Y_1 response.

Table 3: Flowability parameters for all designed formulations

Formulation code	Flowability parameter			USP flow properties
	Hausner ratio	Carr's index	Angle of repose	
F1	1.24	19.57	30.10	Excellent
F2	1.33	25.00	32.72	Good
F3	1.25	19.79	30.54	Excellent
F4	1.31	23.50	33.10	Good
F5	1.27	21.54	29.92	Excellent
F6	1.26	20.83	31.60	Good
F7	1.47	32.18	35.39	Good
F8	1.31	23.81	34.77	Good
F9	1.33	25.00	32.41	Good
F10	1.28	21.88	29.48	Excellent
F11	1.30	23.10	35.14	Good
F12	1.35	25.81	33.25	Good
F13	1.24	19.44	30.98	Excellent
F14	1.25	19.89	29.78	Excellent
F15	1.24	19.47	29.92	Excellent

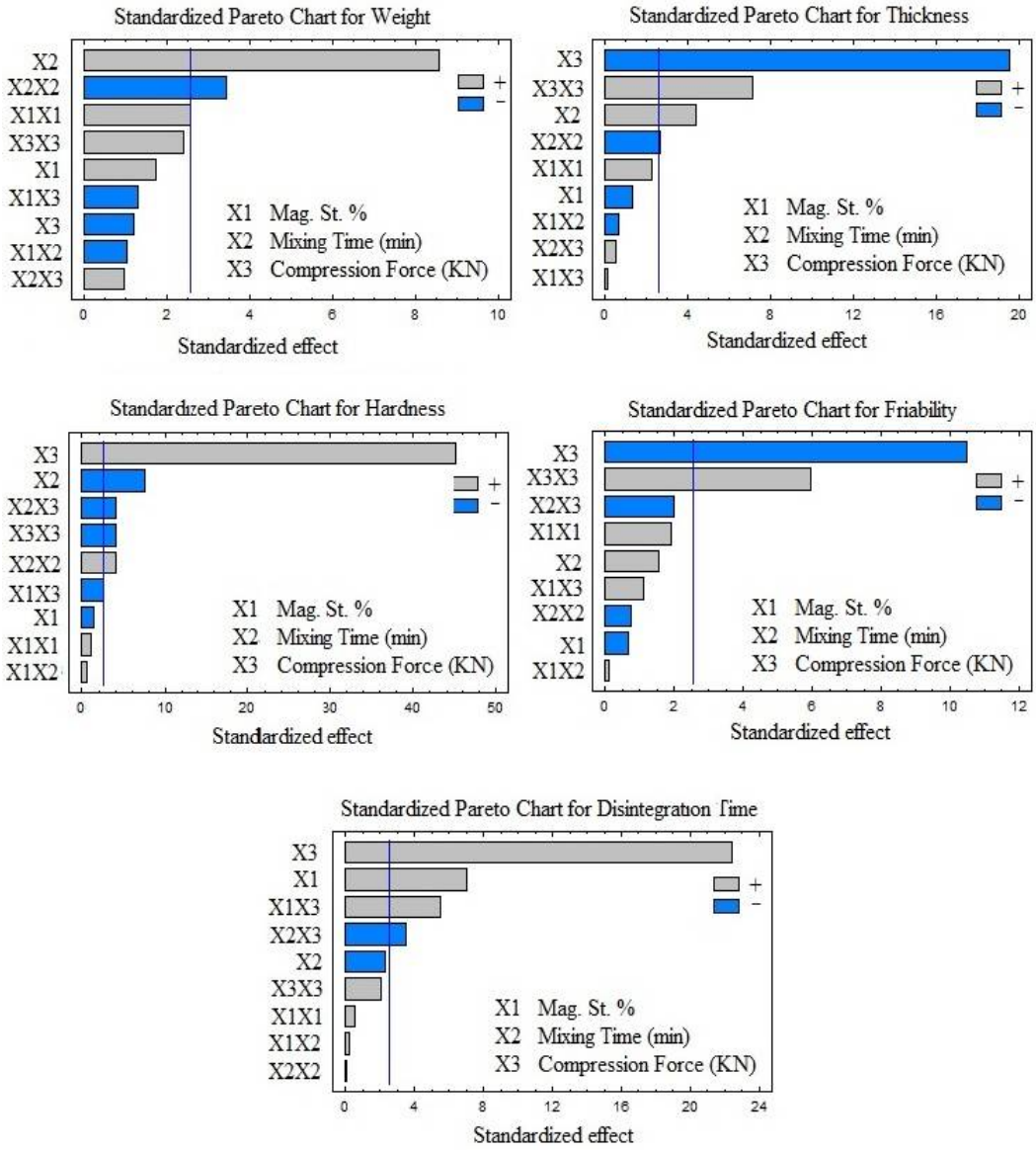

Figure 1: The Pareto charts that represent the relationship of various levels of independent factors to achieve fixed values of Y_{1-5} responses

Y_1 =310.962 – 11.9428X_1 + 1.33677X_2 – 1.96732X_3 + 11.2833X_1^2 – 0.186957X_1X_2 – 0.55X_1X_3 – 0.0285759X_2^2 + 0.0178261X_2X_3 + 0.104833 X_3^2 …… (4)

where X_1^2, quadratic term of lubricant concentration; X_2^2,quadratic term of mixing time; X_3^2, quadratic term of compression force; X_1X_2, interaction between lubricant concentration and mixing time; X_1X_3, interaction between lubricant concentration and compression force; X_2X_3, interaction between mixing time and compression force; Y_1, tablet weight variation (mg); Y_2, tablet thickness (mm); Y_3, tablet hardness (Kp); Y_4, friability (%); and Y_5, *in vitro* disintegration time (sec).

Table 4 and Figures 1 – 3 indicate that P_{value} of X_2 <0.05 and the F_{ratio} was 73.47 (highest value) so it had a significant effect. The P_{values} of X_1 and X_3 were >0.05 and the F_{ratios} were 3.03 and 1.45 (lowest values) so they had an insignificant effect. Moreover, fluoxetine content uniformity within all ODT formulations ranged from 97.72 ± 2.97 to 103.6 ± 1.85 %. Therefore, fluoxetine content distributed homogeneously throughout all suggested prepared formulations.

Tablet thickness (Y_2) measurements were displayed in Tables 2, 4 and Figures 1 – 3. Y_2 ranged from 4.08mm to 4.76mm with F9 and F8, respectively. Pareto chart and estimates calculated showed the priority effect of X_3 over other independent variables, the bars of X_3 and X_2 extended after the reference line accompanied with a negative coefficient of X_3 and positive coefficient of X_2. The relatively larger coefficient of these variables is seen in the regression equation for Y_2 as shown below (Eq. 5):

Y_2 = 5.40669 – 0.355652X_1 + 0.015534X_2 – 0.161598X_3 + 0.17X_1^2 –0.00217391X_1X_2 + 0.001X_1X_3 – 0.000378072X_2^2 + 0.000173913X_2X_3 + 0.0054X_3^2 ……(5)

Calculated *p*-values were < 0.05, plus the F_{ratios} were 19.1 and 381.14 for X_2 and X_3 respectively. Therefore, X_3 had the highest priority effect than other independent variables and accompanied by an inverse proportional effect on Y_2 while X_2 was in the second priority effect. Whereas *p*-value of X_1 was > 0.05 and it accompanied with a very low F_{ratio} (1.85). Consequently, increasing X_2 and X_3 and led to the decreasing of Y_2.

Tablet hardness responses (Y_3) were displayed in Tables 2, 4 and Figures 1 – 3. The lowest Y_3 was reported with F8 (1.2 Kp) but the highest Y_3 was reported with F9 (8.2 Kp). Additionally, the Pareto chart showed the variables of X_2 and X_3 bars were extended after the reference line and the relatively larger coefficient for these terms is shown in the regression equation as below (Eq 6).

Y_3 = –2.74719 – 0.0923913X_1 – 0.063138X_2 + 1.02967X_3 + 0.35X_1^2 + 0.00869565X_1X_2 – 0.09X_1X_3 + 0.00274102X_2^2 – 0.00608696X_2X_3 – 0.0145X_3^2 ……..(6)

X_3 exhibited positive coefficient while X_2 acquired negative coefficient. The *p*-values for X_2 and X_3 were < 0.05 while *F* ratios was 57.3 and 2044.8, respectively, indicating a significant effect of those variables on Y_3 while the calculated P_{value} of X_1 was >0.05 and the F_{ratio} was very low (1.94). Therefore, Y_3 was closely related to the increase of X_2 and X_3 [29].

Table 4: Calculated estimates, *P-values* and *F-ratios* for $Y_{1–5}$ responses

Response		X_1	X_2	X_3	X_1^2	X_1X_2	X_1X_3	X_2^2	X_2X_3	X_3^2
Y_1	Estimate	2.6	12.8	–1.8	5.642	–2.15	–2.75	–7.558	2.05	5.242
	F_{ratio}	3.03	73.47	1.45	6.59	1.04	1.70	11.82	0.94	5.69
	P_{value}	0.142	0.0004*	0.282	0.050	0.355	0.250	0.019*	0.376	0.063
Y_2	Estimate	–0.035	0.113	–0.503	0.085	–0.025	0.005	–0.1	0.02	0.27
	F_{ratio}	1.85	19.10	381.14	5.03	0.47	0.02	6.97	0.30	50.79
	P_{value}	0.232	0.007*	0.0001*	0.075	0.523	0.896	0.046*	0.606	0.001*
Y_3	Estimate	–0.175	–0.95	5.675	0.175	0.1	–0.45	0.725	–0.7	–0.725
	F_{ratio}	1.94	57.30	2044.8	0.90	0.32	6.43	15.40	15.56	15.40
	P_{value}	0.222	0.0006*	0.0001*	0.387	0.598	0.052	0.011*	0.011*	0.011*
Y_4	Estimate	–0.117	0.273	–1.815	0.488	0.025	0.27	–0.193	–0.49	1.5225
	F_{ratio}	0.46	2.48	110.07	3.67	0.01	1.22	0.57	4.01	35.75
	P_{value}	0.527	0.176	0.0001*	0.114	0.923	0.320	0.484	0.102	0.002*
Y_5	Estimate	7.64	–2.525	24.265	0.879	0.325	8.415	–0.181	–5.435	3.319
	F_{ratio}	49.83	5.44	502.69	0.30	0.05	30.23	0.01	12.61	4.34
	P_{value}	0.0009*	0.067	0.0001*	0.605	0.840	0.002*	0.914	0.016*	0.092

** Significant effect of factor on individual response*

Likewise, tablet friability (%) responses (Y_4) were displayed in Tables 2 and 4 and Figures 1 – 3. It ranged from 0.06–2.5% (F9 and F8 respectively). The X_3 had an inverse effect on Y_4 where its bar extended after the reference line and the relatively larger coefficient for this term is shown in the regression equation as below (Eq. 7):

$$Y_4 = 5.84405 - 2.63685X_1 + 0.0719329X_2 - 0.786978X_3 + 0.975X_1^2 + 0.00217391X_1X_2 + 0.054X_1X_3 - 0.000727788X_2^2 - 0.00426087X_2X_3 + 0.03045X_3^2 \quad \text{.....(7)}$$

However, X_1 and X_2 had an insignificant effect on Y_4 response. Furthermore, the P_{values} were <0.05 and the F_{ratio} (110.07) were the highest among all other variables effect. On the other hand, the P_{values} for X_1 and X_2 were >0.05 and the F_{ratios} were 0.46 and 2.48 respectively, which were lower than the value of X_3 (110.07) reported. This indicated that X_1 and X_2 had insignificant and low priority effect on Y_4. Therefore, the tablets that were prepared at stronger X_3 presented lower Y_4 due to the hardness and thickness [29].

The time of disintegration (Y_5) responses were seen in Tables 2, 4 and Figures 1 – 3. F4 exhibited the lowest Y_5 (11.42 s) but the highest was noticed with F10 (45.45 s) in which the Y_5 regression equation (Eq. 8):

$$Y_5 = 11.0438 - 13.0882X_1 + 0.353025X_2 + 0.0538551X_3 + 1.75833X_1^2 + 0.0282609X_1X_2 + 1.683X_1X_3 - 0.00068368\ X_2^2 - 0.0472609X_2X_3 + 0.0663833\ X_3^2 \quad \text{.....(8)}$$

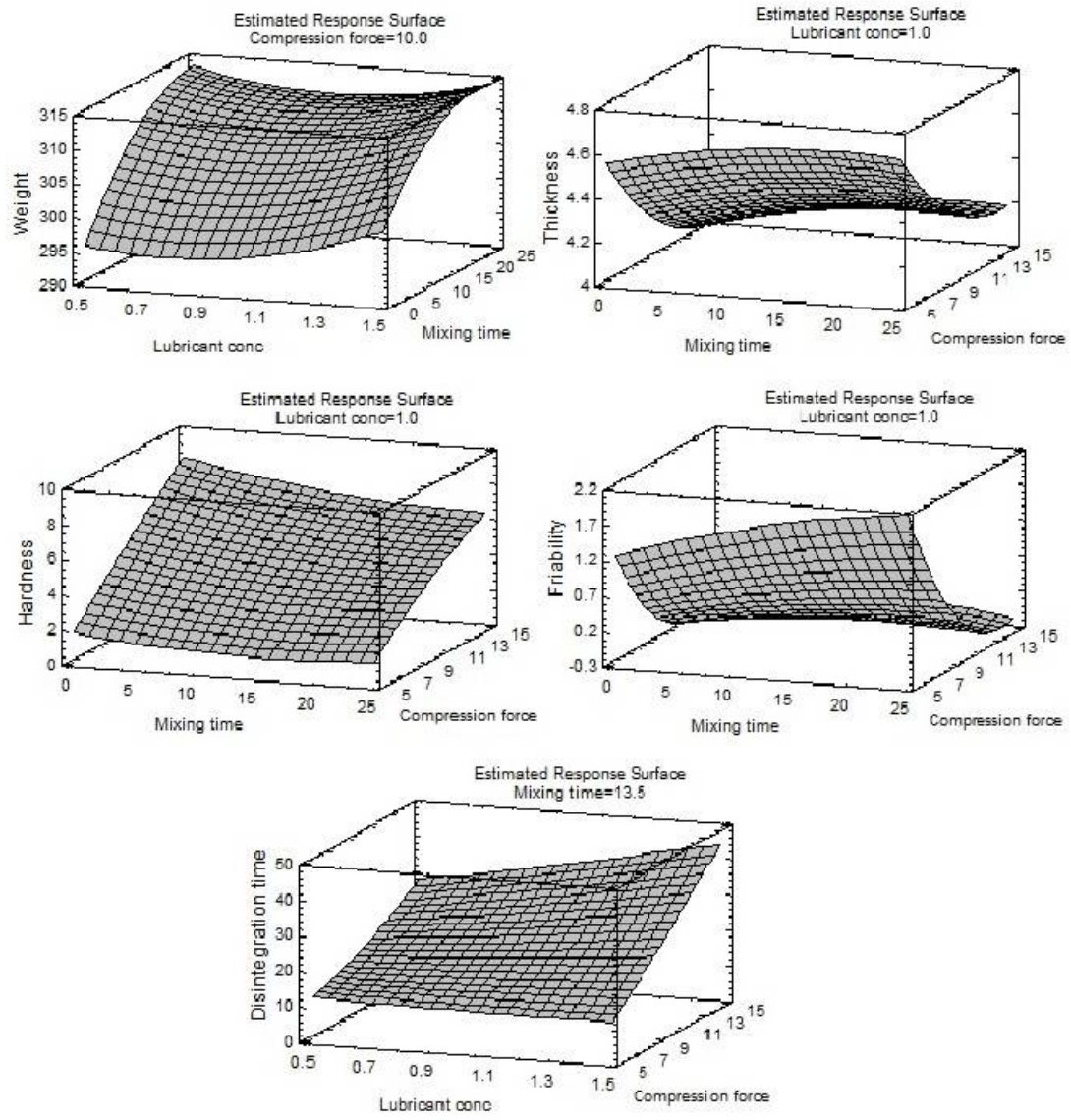

Figure 2: 3D response surface plots represent the relationship of different levels of independent factors to achieve the fixed values of Y_{1-5} responses

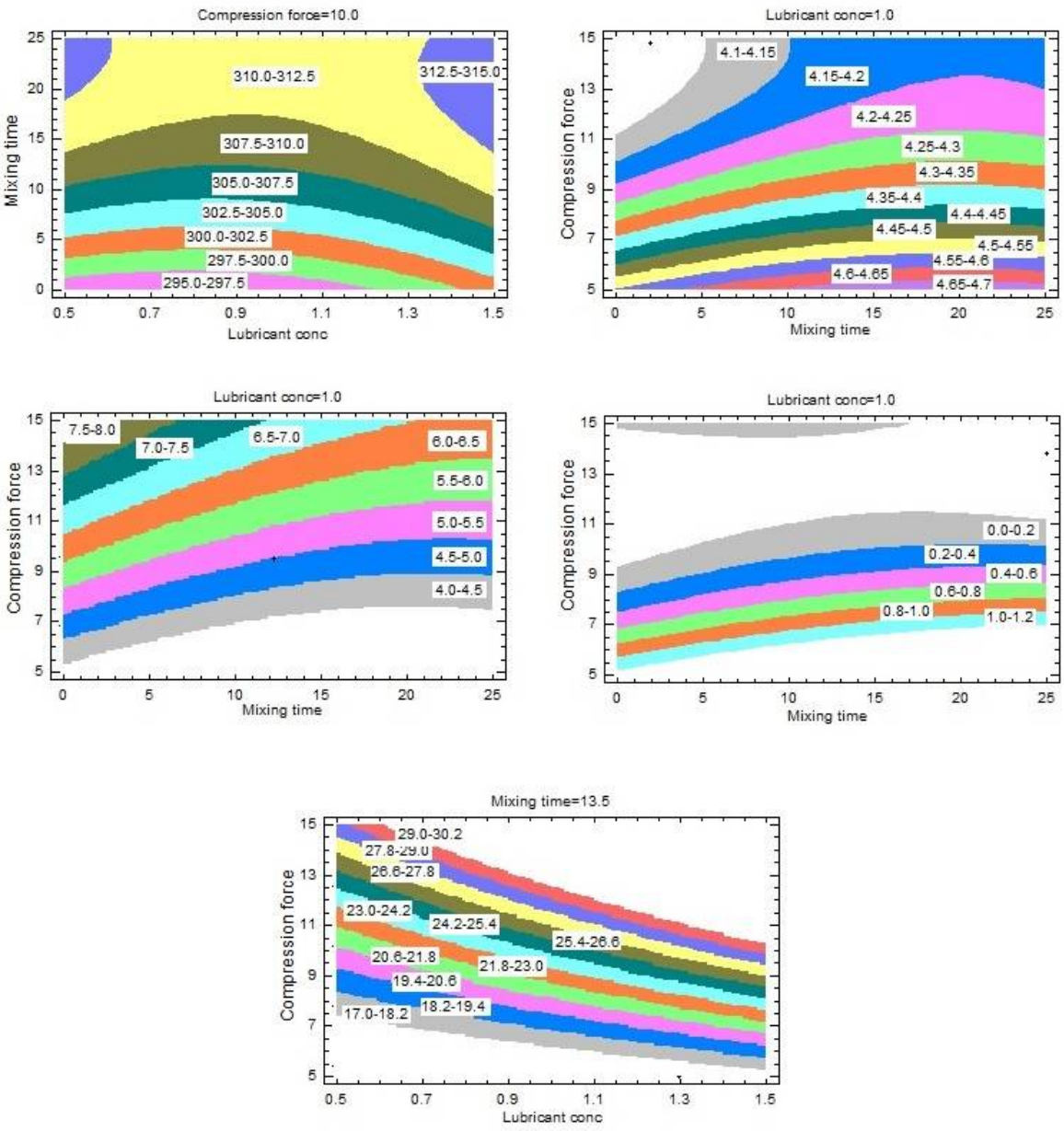

Figure 3: Contours surface response plots represent the relationship of different levels of independent factors to achieve the fixed values of Y_{1-5} responses

The positive coefficient of X_1 and X_3 demonstrated direct proportional effect plus high priority effect of X_3 compared to X_1 on Y_5 as displayed. The P_{values} of X_1 and X_3 were < 0.05. The P_{value} of X_2 was > 0.05 which indicated an insignificant effect on Y_5. Additionally, the F_{ratios} of X_1, X_2, and X_3 were 49.83, 5.44, and 502.69 respectively. These results are in accordance with the findings of other works [29].

All formulations achieved T_{50} (time of 50 % of fluoxetine release) within the first minute while T_{80} (time of 80 % of fluoxetine release) was achieved by F4 and F8 within 1 min. The dissolution of the 15 formulations after 5 min ranged from 71.45 - 96.73 %. After 10 min, the values ranged from 78.56 – 100.00 %; while after 15 min, dissolution from almost all formulations approximately 100 %. Figure 4 showed the dissolution profile of selected formulations. This selection is based on the fact that these selected formulations showed the effect of X_1, X_2, and X_3 employed without repeating the results for the remaining formulations that display the effect of independent variables.

DISCUSSION

The powder blends displayed acceptable flowability property which ranged from good to

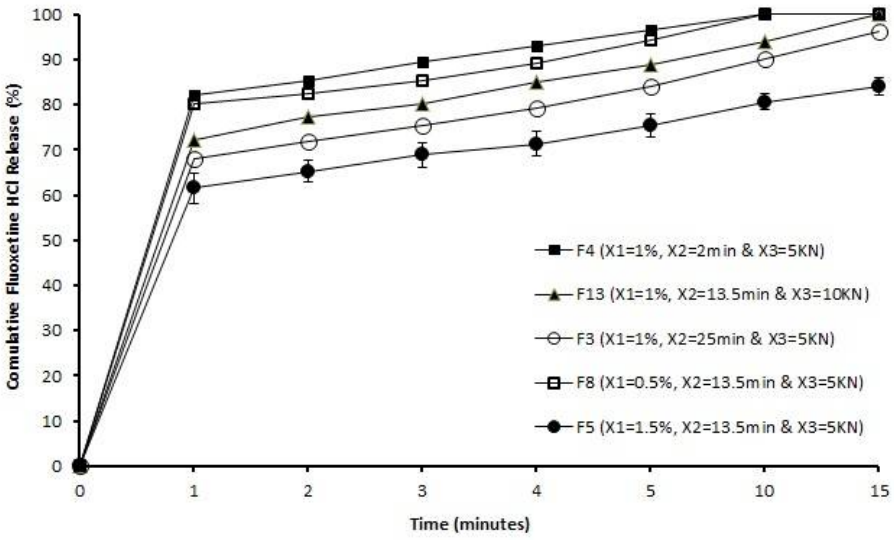

Figure 4: Dissolution profiles for some selected formulations

excellent [23,24]. Magnesium stearate particles formed a thin layer covering the other powder particles that improved the powder flowability properties, especially with higher concentration (1.5 %). The longer mixing time (13.5 and 25 min) enabled the lubricant particles to fill all groves over the powder blend particles surface and form an intact thin layer over the particles surfaces [9].

Tablet weight variation is closely correlated with the increase of lubricant mixing time due to the presence of lubricant material like magnesium stearate within the powder blend. Besides, the mixing time allowed the lubricant particles to spread efficiently throughout the tablet ingredients particles forming a thin layer over these particles, that leads to minimum particles interaction and friction and consequently improving the flowability properties [7]. The punches spaces of tablet press machine were filled with powder particles without pressure only with the powder flowability effect. Therefore, excellent powder flowability property is considered as a requirement for the successful direct compression technique [9]. Excellent powder flowability property reduced the particle friction so particles moved easily over each other. So, the particle-particle spaces might be reduced to its minimum, leaving more spaces that could be filled with excess particles between the punches spaces instead of air that might explain the tablet weight increase. At the same time the ODTs weight is controlled by the punches spaces that were adjusted before commencing the compression process. Consequently, the ODTs weights were not very noticeable, but they were around 300 mg ± 7.5 % [24].

Tablets thickness is mainly influenced by the increase in compression force and the decrease of mixing time since the decrease of powder flowability property leads to the decrease of particles content. Tablet hardness is also strictly associated with the increase of compression force and the decrease of mixing time as reported by Andries *et al* [29]. Tablet friability is affected by the compression force employed during tablets pressing in which leads to harder tablets. Disintegration time is thoroughly related to the increase in lubricant concentration and compression force, but it is not influenced by the length of mixing time. It might be due to the decrease of tablets friability % and hardness as reported tby others [29].

Fluoxetine tablet content was uniformly distributed throughout the formulation and the direct compression technique displayed an efficient procedure for the manufacturing of fluoxetine HCl ODTs.

The fluoxetine release (%) was very high within the first minute of dissolution, then T_{80} was noticed within 5 min of dissolution with those formulations that had the smallest lubricant concentration, shortest mixing time, and lowest compression force (Figure 4). Consequently, lubricant concentration, mixing time, and compression force influenced the fluoxetine release (%) due to the hydrophobic property of magnesium stearate, since it forms a layer over the particulates and stronger compression force increases the tablets hardness as reported by others [29].

The goal of this work was to prepare an optimized fluoxetine ODTs formula with an average weight of 300 mg ± 7.5%, minimum

Table 5: The suggested optimum formula plus predicted, observed responses, residuals and prediction error %

Independent Factors	Optimum	Dependent Factors	Predicted	Observed	Residuals	Prediction Error (%)
X_1	0.86	Y_1	309.15	308.2	0.95	0.31
X_2	15.3	Y_2	4.28	4.3	– 0.02	– 0.4
X_3	10.6	Y_3	4.7	4.6	0.1	2.13
		Y_4	0.135	0.129	0.006	4.44
		Y_5	22.4	21.6	0.8	3.57

tablet thickness, friability (%), and disintegration time, but accompanied with maximum tablet hardness. The optimum responses of the variables were gained through graphical and numerical analysis by means of statistical Statgraphics® software and based on the principle of desirability [30]. The Box-Behnken design has suggested an optimized formula as in Table 5.

Therefore, the suggested formula was prepared and then characterized as done before. The experimental results were compared to the design predicted results by calculating the residual and residual error (%) in order to validate the Box-Behnken design suggestion. The residual differences were 0.95 mg, –0.02 mm, 0.1 Kp, 0.006 %, and 0.8 s respectively, and the prediction errors (%) were 0.31, –0.4, 2.13, 4.44, and 3.57 %, respectively. The results showed an insignificant difference (t-test, P_{value} > 0.05) between the predicted and experimental responses (Table 5). The suggested optimal formula showed the best-fitted formula amongst other formulae according to the prediction error (%) and/or residual results which were below 5 % and could be considered negligible.

CONCLUSION

Fluoxetine ODTs have been successfully developed and improved by a Box-Behnken experimental design, and prepared using direct compression technique. Variables including lubricant concentration, mixing time, and compression force have a quantitative effect on the weight variation, thickness, hardness, friability (%), and *in vitro* disintegration time which could be predicted by Box-Behnken design.

The experimental values of the improved formula were close and in line with the predicted values that verified the integrity of the developed fluoxetine ODTs formulation. Finally, this optimized and developed antidepressant drug, fluoxetine HCl, ODTs formulation will achieve numerous targeted benefits such as rapid onset of action, high bioavailability, ease of administration, and patients' convenience, especially for those with swallowing difficulties regardless of age.

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