Understanding the formulation variables of orodispersible tablets containing simvastatin solid dispersion using Box-Behnken design

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Abstract

Simvastatin is a well established oral anti-hypercholesterolemic agent. This study aimed to formulate simvastatin as orodispersible tablets. The drug was incorporated as a solid dispersion using Pluronic® F68 as carrier. Croscarmellose Na was used as superdisintegrant, microcrystalline cellulose as filler, PVP K-30 as binder and 1:1 magnesium stearate/talc mixture as lubricant. Box-Behnken design was adapted to explore the main and interaction effects of three independent formulation variables on the prepared tablets, namely superdisintegrant concentration (X_1), lubricant mixture concentration (X_2), and binder concentration (X_3). A total of 13 tablet formulations were fabricated in addition, to two replicates of the center point to assess variability and experimental error. The selected dependant variables were the *in vitro* and *in vivo* disintegration times, dissolution rate at 4 min, and dissolution efficiency after 30 min. Wetting time, drug content, hardness and friability were also evaluated. Tablet formula, composing of 12% superdisintegrant, 2% lubricant mixture and 3% binder, showed the highest dissolution rate with an acceptable disintegration time (43 sec), hardness, and friability and was chosen as the best formula. An accelerated stability study was conducted for 6 months at 40°C/75% RH. Results showed no significant changes in any of the tested parameters.

Introduction

Simvastatin is a potent inhibitor of 3-hydroxy-3-methyl-glutaryl-coenzyme A (HMGCoA) reductase. It is a cholesterol-lowering agent widely used to treat hypercholesterolemia. However, it suffers poor oral bioavailability due to its water-insolubility and extensive first pass metabolism by the CYP450 isoform 3A4, and CYP3A5, in the intestinal wall and liver.[1]

Solid dispersion technique is one of the well established and most successful strategies for increasing the solubility of poorly soluble drugs.[2] Solid dispersions are classified into three generations depending on the carrier type. First generation solid dispersions are those prepared using crystalline carriers like urea and sugars. Second generation solid dispersions depend on amorphous carriers such as polyvinyl pyrrolidone (PVP) and polyethylene glycols (PEG). Carriers for third generation solid dispersions are surfactants such as Inutec® SP1 and Pluronic® F-68 or surfactant-amorphous polymer mixtures. Literature shows some examples for preparing Simvastatin solid dispersions were applying different carriers and methods of preparation.[3-5]

Orodispersible tablets are those disintegrating or dissolving in less than three minutes in the mouth.[4] They are easy administered leading to better patient compliance.[5] Orodispersible tablets can be prepared by lyophilization, molding or compression. However, formulation studies are essential to obtain tablets showing appropriate disintegration time along with acceptable physical characters like friability and hardness.

Box-Behnken design is a rotatable or nearly rotatable second-order design based on a three-level incomplete factorial design. This design is suitable for exploring quadratic response surfaces and constructing second order polynomial models. The application of such design to pharmaceutical formulation development has been demonstrated to be efficient and satisfactory to understand the relationship between independent and dependent variables in the formulation processes.[6]

This study aimed to formulate solubilized simvastatin as orodispersible tablets by direct compression. Work included exploring the effect of different formulation variables on the properties of the prepared tablets adapting a three level three factors Box-Behnken design.

Materials and Methods

Materials

Simvastatin (Ranbaxy Laboratories, Dewas, India) Pluronic® F-68 was purchased from MP Biomedicals, INC.CO., France, Croscarmellose Na (FMC Bio Polymer, Bruss els, Belgium), colloidal silicon dioxide (Aerosil®) from Röhm Pharma, GmbH, Germany, talc and magnesium stearate (Adwic, El-Nasr Pharmaceutical Chemicals Co., Egypt), Aspartame (Fluka AG, Buchs, Switzerland), HPLC grade Acetonitrile (Sigma-Aldrich Co, Germany) and microcrystalline cellulose (MMC) from Morgan chemical IND.CO, Egypt. All other chemicals and solvents were of analytical grade.

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Experimental design

Box-Behnken design was adapted using three factors and three levels. Table 1 shows the tested factors and their levels. Equation (1) shows the non-linear quadratic model generated by the design:

$$Y=b_0+b_1X_1+b_2X_2+b_3X_3+b_{12}X_1X_2+b_{13}X_1X_3+b_{23}X_2X_3+b_{11}X_1^2+b_{22}X_2^2+b_{33}X_3^2$$

where Y is the measured response associated with each factor level combination; b_0 is an intercept; b_1– b_{33} are the regression coefficients; X_1, X_2 and X_3 are the factors studied; and The terms X_iX_i and X_i^2 (i=1, 2 or 3) represent the interaction and quadratic terms respectively.[7] A total of 13 distinct formulations were fabricated and tested. In addition, two replicates of the center point were tested to assess variability and experimental error.

Lack of fit test was used to assess the fit of the selected model. If the P-value is less than the selected α-level (0.05), evidence exists that our model does not accurately fit the data and the reverse is true.

The goodness of fit of the model was also checked by the determination coefficient (R^2). The R^2 values provide a measure of how much variability in the observed response values can be explained by the experimental factors and their interactions. The R^2 value is always between 0 and 1. The closer the R^2 value to 1, the stronger the model and the better it predicts the response.[8]

The adjusted determination coefficient (R_a^2) corrects the R^2 value for the sample size and the number of terms in the model. If there are many terms in the model and the sample

size is not very large, the (R_a^2) may be noticeably smaller than the R^2.

Response surfaces were constructed to visually present the effect of the formulation variables on drug release. (Design Expert software, version 7.0, Stat-Ease Inc., Minneapolis, U.S.A.).

The significance of independent variables was examined using analysis of variance (ANOVA) for each response at an error probability of 0.05.

Preparation of solid dispersion

Solid dispersion was prepared at 1:5 simvastatin to Pluronic® F-68 ratio by solvent evaporation technique. First, the drug and the carrier were dissolved in 95% ethanol to produce a clear solution by sonication for 30 min. Then, the solvent was removed using a rotary evaporator (Heidolph instrument Model D91126). The resultant mass was pulverized and finally stored in desiccator for further processing.[3]

Preparation of orodispersible tablets

Each tablet contained solid dispersion equivalent to 10 mg simvastatin, 5% w/w aspartame as sweetening agent, 1% w/w Aerosil® as glidant, croscarmellose Na as superdisintegrant, PVP K-30 as binder and a constant weight (500 mg) of microcrystalline cellulose as filler. The different ingredients were accurately weighted and mixed in a mortar. Magnesium stearate and talc were added and mixed. The resulting mixtures were directly compressed using a single-punch tablet press machine (Royal Artist, Bombay, India, circular-flat 17-mm punches). Compression forces were adjusted to produce tablets with hardness range of 5-6 kg.

Evaluation of orodispersible tablets

Physical properties and drug content uniformity

The friability of 10 orodispersible tablets of each formulation was measured at 25 rpm for 4 min (Tablet friabilator digital test apparatus, Model DFI-1; Veego, Bombay, India). Percentage weight loss was calculated for each formula. Ten randomly selected tablets were evaluated for their thickness using tablet micrometer. The relative standard deviation (% RSD) values were calculated. The mean tablet weights and % RSD were recorded using 20 tablets from each formula. Hardness of the tested orodispersible formulations was measured using Monsanto hardness tester, USA. The % RSD values were calculated. Ten tablets from each formulation were pulverized to a fine powder. Accurately weighed aliquots containing an amount of powder equivalent to a single dose were taken in triplicate and assayed spectrophotometrically for simvastatin at λ_{max} of 239 nm.

Wetting time

Five circular filter papers were placed in a Petri dish of 10 cm diameter. Ten milliliters of water containing 0.5% amaranth was added to the Petri dish. A tablet was carefully placed on the surface of the tissue paper in the Petri dish. The time required for water to reach the upper surfaces of the tablets and to completely wet them was recorded using a stopwatch.[9] All measurements were done in triplicates.

In vitro disintegration time

The disintegration time was determined in 900 ml phosphate buffer of pH 6.8 at 37°C using a USP Disintegration Tester (Logan instruments, USA). All experiments were done in triplicates.

In vivo disintegration time

The time for complete disintegration in the mouth was measured in three healthy trained volunteers. Volunteers were asked to rinse their mouths with distilled water prior to the test. Tablets were placed on the tongue and volunteers were allowed to move the tablet against the upper palate of the mouth with their tongues and cause a gentle tumbling action on the tablet without chewing it. The time for complete disintegration without leaving any lumps was taken as end point. After disintegration of tablet in the oral cavity, the tablet contents were spit out and the oral cavity was rinsed with water. Swallowing of saliva was prohibited during the test, and the mouth was rinsed after each measurement. The mean and SD were calculated for each tablet.[10]

In vitro dissolution studies

The dissolution rate of simvastatin from the orodispersible tablets was studied in a rotating paddle apparatus (Vision® Classic 6™ Dissolution Tester, Hanson Research Corporation, California, USA) at 37±0.5°C and 50 rpm in 900 ml phosphate buffer (pH 6.8). Samples were withdrawn through 0.45 µm Millipore filter at different time intervals up to 30 min, and assayed spectrophotometrically for simvastatin at 239 nm. The dissolution experiments were conducted in triplicate. The same procedure were carried out for the commercial available conventional tablets (Zocor®, 10 mg tablets, Astra Zeneca). Dissolution rate was measured after 4 min (DR_{4min}). Dissolution efficiency (DE_{30min}) was calculated according to Khan.[11]

Stability study

The selected tablet formulation was exposed to six months accelerated stability study at 40°C and 75% RH.[12] At the end of one, three and six months, tablets samples were withdrawn and re-evaluated for their hardness and friability. The stability indicating HPLC assay for determination of simvastatin in stored tablets was developed and validated. The *in vitro* dissolution profile was studied and compared to the fresh one by calculating the similarity factor (f_2) using the following equation:[13]

$$f_2 = 50 \times \log\left\{\left[1 + \left(\frac{1}{n}\right)\sum_{t=1}^{n} w_t(R_t - T_t)^2\right]^{-0.5} \times 100\right\}$$

Where *Rt* and *Tt* are the cumulative percent of drug released for reference and test assay at time *t*, respectively, and *n* is the number of time points. The similarity factor fits the result between 0 and 100. It is 100 when the test and reference profiles are identical and tends to 0 as the dissimilarity increases.

Results and Discussion

Experimental design

Box-Behnken design is a useful and efficient tool to obtain an appropriate model with minimum experiments. The evaluated formulations factors were superdisintegrant concentration (X_1), lubricant mixture concentration (X_2), and binder concentration (X_3). The levels of the studied factors were selected based on preliminary studies.

A superdisintegrant was added to attain fast disintegration by breaking up the tablets into smaller fragments.[14] Croscarmellose Na was selected among other superdisintegrants, such as crospovidone and sodium starch glycolate, depending on sufficient preliminary experiments.

Binder concentration is critical in formulating orodispersible tablets. High binder concentration could lead to harder tablets which are difficult to disintegrate. On the other hand using too low quantity of binder could result in friable tablets.[15] Similarly lubricant concentration should be optimized to improve fluidity and filling properties to prevent powder adhesion to punch faces and to minimize die-wall friction without influencing disintegration time.[16] A mixture of 1:1 magnesium stearate and talc was used as a lubrication system.

Table 1 shows the measured responses for all the prepared formulations. The analysis of variance (ANOVA) was conducted to test the significance of the fit of the second-order polynomial equation for the experimental data.[17] Results are given in Tables 2 and 3.

High values of R^2 and R_a^2 ensured a satisfactory adjustment of the polynomial model to the experimental data Table 2.

Preparation of orodispersible tablets

The 1:5 simvastatin/Pluronic solid dispersion was used due to its stated enhancement

in simvastatin dissolution rate compared to the plain drug.[3] However, direct compression of the obtained solid dispersion produced tablets with long disintegration times (exceeding 8 minutes) due to its waxy and cohesive nature. Microcrystalline cellulose was added as filler in large quantity to enhance tablet disintegration. Microcrystalline cellulose provides good dispersion and uniform mixing with drugs, acts as disintegrating agent and shows good compressibility.[18]

Evaluation of orodispersible tablet

Physical properties and drug content uniformity

Table 4 shows the physical properties of the prepared tablet formulations. The prepared tablets showed acceptable weight uniformity (%RSD ranged from 0.181 to 0.973). The mean thickness values ranged from 2.30-3.13mm with %RSD less than 3.464. While hardness ranged from 5-6.1 kg with %RSD values less than 5.33. All the prepared tablet formulations recorded acceptable friability values except formulations1, 2, 9 and 12 which showed friability percentage more than 1%. The drug content ranged from 96.98 to 102.57% with %RSD of 0.755 to 5.021, which obeys the pharmacopeial limits of 90 -110%.

Wetting time

Wetting time gives an insight into the disintegration properties of the tablets because it is closely related to the inner structure of the tablets and to the hydrophilicity of the excipients. All the tested formulations recorded quick wetting (wetting times ≤30 sec.), Table 4.

In vitro disintegration time

The *in vitro* disintegration time values of the prepared formulations were less than 60 sec. (Table 1).

The ANOVA analysis of the regression models showed that the quadratic model was not significant for the *in-vitro* disintegration times. However significant correlation still present and the linear model was the most suitable for evaluation. Such statement indicates that the variation in disintegration time could be attributed to changes in the independent factor settings over the range of study without any curvature or interaction between the experimental factors. Relatively bad correlation between the *in vitro* disintegration time and independent variables was observed (low R^2 and R_a^2). Similar findings were previously reported and was attributed to the imprecise method used to determine the disintegration time of the tablets.[19,20] And thus *in vivo* disintegration time was estimated.

In vivo disintegration time

Table 1 shows that the *in vivo* disintegration time values were higher than their corresponding *in vitro* ones. This could be attributed to the large volume of disintegration medium in the disintegration test apparatus which could lead to faster hydration and swelling of the superdisintegrant.

The ANOVA analysis of the regression models showed that the quadratic model was not significant for in-vivo disintegration time (Table 2). However significant correlation still present and the linear model was the most suitable for evaluation. The *R*-Squared (R^2) statistic indicates that the model as fitted explains 85.21% of the variability in the results. The adjusted *R*-squared (R_a^2) statistic is 81.19% (Table 2).

The ANOVA Table 3 partitions the variability in case of *in vivo* disintegration time into separate pieces for each of the effects. It then tests the statistical significance of each effect by comparing the mean square against an estimate of the experimental error. In this case, the three tested factors recorded *P-values* less than 0.05, indicating that they are significantly different from zero at the 95% confidence level (Table 3). The standardized main effect (SME) values reveal that both the binder and lubricant have positive effects while superdisintegrant produces a negative effect on the *in vivo* disintegration time.

The relationship between the *in-vivo* disintegration time and the formulation factors was statistically significant and come in agreement with previously reported data which demonstrated that; increasing tablet binders[21] and hydrophobic lubricants[22] delay tablets disintegration while the reverse is true with superdisintegrant[23] (Table 3). No significant interaction was observed between any of the evaluated factors.

In vitro dissolution studies

One of our important goals was the maximization of simvastatin release within the first minutes of dissolution. Dissolution profiles are presented in Figures 1-3. As shown in Table 1, the rate of drug release at 4 min ranged from 8.465-22.077 (compared to 1.51 with Zocor®) indicating significant enhancement. The dissolution efficiency values of simvastatin from the prepared orodispersible

Table 1. Composition and evaluation parameters of the prepared tablet formulations according to Box-Behnken design.

	Independent variables			Measured responses			
Formulations	Superdisintegrant (%) X_1	Lubricant (%) X_2	Binder (%) X_3	*In vitro* disintegration time (sec) Y_1	*In vivo* disintegration time (sec) Y_2	*DE_{30min} (%) Y_3	DR_{4min} Y_4
F 1	4	1	3	55	65	78.996	16.643
F 2	12	1	1.5	21	49	80.394	19.628
F 3	4	1	0	10	45	49.677	8.465
F 4	20	2	1.5	25	45	68.62	13.19
F 5	12	0	3	30	54	82.16	19.135
F 6	20	1	0	25	36	71.388	16.844
F 7	12	1	1.5	30	46	80.746	20.664
F 8	12	0	0	20	39	82.727	19.153
F 9	12	1	1.5	25	45	80.135	19.918
F 10	20	0	1.5	25	30	73.968	16.754
F 11	12	2	3	43	59	92.124	22.077
F 12	12	2	0	16	50	77.893	16.32
F 13	4	2	1.5	10	70	72.272	15.279
F 14	20	1	3	32	35	82.412	18.353
F 15	4	0	1.5	10	50	66.743	13.098

DE, dissolution efficiency; DR, dissolution rate.

Table 2. Summary of results of: (a) model analysis, (b) lack of fit and (c) R-square analysis for measured responses.

Source	Y_1		Y_2		Y_3		Y_4	
	SS	P>F	SS	P>F	SS	P>F	SS	P>F
(a) Model analysis								
Mean *vs*. total	9475.267		34368.27		86679.73		4352.77	
Linear *vs*. mean	1060.75	*0.0471*	1438.25	*<0.0001*	471.0882	0.1702	46.92829	0.3009
2FIa *vs*. linear	433.25	0.2170	125.5	0.1163	167.9891	0.6047	27.70362	0.5474
Quadratic *vs*. 2FI	366.3167	0.1888	62.56667	0.2819	538.7449	0.0416	85.33872	*0.0102*
Cubic *vs*. quadratic	218.75	0.2257	52.75	0.2040	150.1104	0.0019	11.30653	0.0714
Residual	40.66667		8.666667	0.188365		0.572087		
Total	11595		36056		88007.85		4524.62	
(b) Lack of fit								
Linear	1018.317	*0.1616*	240.8167	*0.1471*	856.8444	0.0010	124.3489	0.0204
2FI	585.0667	0.1826	115.3167	0.1954	688.8553	0.0008	96.64525	0.0176
Quadratic	218.75	0.2257	52.75	0.2040	150.1104	0.0019	11.30653	*0.0714*
Cubic	0		0		0		0	
Pure error	40.66667		8.666667		0.188365		0.572087	
	R^2	R_a^2	R^2	R_a^2	R^2	R_a^2	R^2	R_a^2
(c) R^2analysis								
Linear	*0.500417*	*0.364167*	*0.852178*	*0.811863*	0.354703	0.178713	0.273078	0.074827
2FI	0.704806	0.48341	0.926539	0.871442	0.481189	0.092081	0.434287	0.010002
Quadratic	0.877618	0.657331	0.96361	0.898108	0.886834	0.683134	*0.930878*	*0.806458*
Cubic	0.980815	0.865706	0.994865	0.964054	0.999858	0.999007	0.996671	0.976697

Table 3. Standardized main effects of the factors on the responses.

	Y_1			Y_2			Y_3			Y_4		
	Coefficient estimate	*P*-value	SME[a]	Coefficient estimate	*P*-value	SME	Coefficient estimate	*P*-value	SME[a]	Coefficient estimate	*P*-value	SME
B0	25.13333	0.0471	9.92	47.86667	< 0.0001	38.93	80.42553	0.0599	25.4075	20.06999	0.0196	22.55
b1	2.75	0.4447	0.79	-10.5	< 0.0001	-6.24	3.587423	0.1234	1.850695	1.456855	0.0442	2.67
b2	1.125	0.7518	0.32	6.375	0.0030	3.79	0.66393	0.7459	0.342511	-0.15939	0.7817	-0.29
b3	11.125	0.0084	3.21	5.375	0.0086	3.19	6.750972	0.0176	3.48272	1.928265	0.0166	3.54
b12	----	----	----	----	----	----	-2.71937	0.3668	-0.99199	-1.43609	0.1214	-1.86
b13	----	----	----	----	----	----	-4.57356	0.1561	-1.66837	-1.66704	0.0829	-2.16
b23	----	----	----	----	----	----	3.699302	0.2351	1.349451	1.443785	0.1199	1.87
b11	----	----	----	----	----	----	-11.5659	0.0098	-4.05354	-4.79239	0.0019	-5.97
b22	----	----	----	----	----	----	1.541609	0.6122	0.540294	-0.69738	0.4244	-0.87
b33	----	----	----	----	----	----	1.759065	0.5645	0.616507	-0.2012	0.8119	-0.25

Standardized main effects (SME) were calculated by dividing the main effect by the standard error of the main effect.

Table 4. Evaluation parameters for the prepared tablet formulations.

Formulations	(Mean±SD) Average friability (%)	Average thickness (mm)	Average weight (mg)	Average hardness (Kg)	Average drug (%)	Average time (sec)
F1	12.200	2.45±0.05	636.20±5.22	5±0.08	98.26±2.34	10±1.07
F2	1.224	2.91±0.06	699.03±1.33	6±0.07	99.17±3.75	12±0.91
F3	0.115	2.30±0.00	614.71±4.19	5.5±0.00	98.87±2.47	7±0.87
F4	0.282	3.03±0.05	782.84± 2.39	6±0.32	96.98±4.87	15±1.57
F5	0.312	2.72±0.08	706.24±2.84	6±0.09	100.26±4.13	7±0.69
F6	0.197	2.96±0.08	759.50±3.62	5.8±0.07	99.48±3.54	8±1.09
F7	0.338	2.85±0.07	699.76±3.69	5±0.03	98.45±0.98	16±0.71
F8	0.706	2.71±0.03	680.88±3.95	6±0.05	97.22±1.02	6±0.86
F9	6.290	2.90±0.00	697.14±3.89	5.1±0.02	101.13±2.12	14±2.14
F10	0.020	2.98±0.06	763.55±1.38	5.9±0.08	99.42±4.64	5±0.93
F11	0.375	2.76±0.07	723.07±3.90	5±0.04	100.14±3.12	30±1.86
F12	2.037	2.68±0.03	698.21±2.68	5±0.02	102.57±3.22	5±0.37
F13	0.114	2.50±0.08	636.96±2.44	5.1±0.03	97.98±1.06	5±0.77
F14	0.414	3.13±0.07	789.80±4.01	5±0.07	99.24±0.75	10±1.15
F15	0.084	2.50±0.08	618.54±6.01	5±0.06	97.54±4.16	5±0.95

tablets were 1.8-2.5 fold greater than that from the commercial conventional tablets (36.5%). Such significant enhancement in both the rate and extent of simvastatin *in vitro* release suggests better bioavailability *in vivo*.

The ANOVA table implies the significance of the quadratic model to evaluate the results. Furthermore, for the full quadratic model, the *P*-value for lack of fit was 0.0714 suggesting that this model adequately fits the data (Table 2). The *R*-Squared (R^2) statistic indicates that the model as fitted explains 93.091% of the variability in drug release rate at 4 min .The adjusted *R*-squared (R_a^2) statistic is 80.65% (Table 2).

Only the superdisintegrant concentration (X_1) and binder concentration (X_3) showed significant effect on the release rate at 4 min (*P*-value=0.0442 and 0.0166, respectively) (Table 3). However, the binder content effect was more pronounced (see SME values).

The significance of the second order relation between the drug release rate at 4 min and the superdisintegrant concentration indicates the presence of significant curvature between those two variables (Figures 1, 2 and 3). Increasing the superdisintegrant concentration enhanced the dissolution rate for superdisintegrant concentrations ≤12% (positive effect) Such findings are in agreements with earlier reports,[24,25] where high superdisintegrant concentrations improve the rate and extent of liquid uptake and penetration into the tablets, the tablets broke up quicker exposing the drug particles to the dissolution medium and improving the contact between drug particles and solvent molecules. While, further increase in superdisintegrant concentration to 20% decreased the release rate of the drug from the tablets. This effect could be attributed to the binding properties of croscarmellose Na. By croscarmellose Na proportions lower than 12%, the dissolution improvement effect is more important, while thereafter the binding properties overcome.[26] In addition, large concentration of superdisintegrant could compete with the drug for the solvent while no significant decrease in disintegration time was achieved.

Increasing the binder concentration significantly increased the dissolution rate. In addition to being a binder, PVP K30 is widely used as water soluble carrier to increase the solubility of poorly soluble drugs. As binder, PVP is expected to hinder the dissolution of the drug by increasing the hardness of tablet and hence delaying its disintegration. However in this study such effect was minimized by maintaining the hardness of all tablets constant (5-6 kg). Similar findings were previously reported.[27-30]

The lubricant mixture concentration had no significant effect on dissolution rate (Table 3). This could be attributed to the small percent used here and to the presence of large quantity (500 mg) of microcrystalline cellulose which is thought to dilute the negative impact of lubricants on drug dissolution.

Most of the studies on how magnesium stearate affected tablet dissolution suggested that lubricants had some negative effects on the *in vitro* dissolution of immediate release tablets, with the more hydrophobic lubricants (*e.g.*, Magnesium stearate) seemingly showing more pronounced deleterious effects. A number of experimental findings[31-33] have led to the theoretical conclusion that the observed deleterious effect of lubricants on dissolution is due to their large surface area which, in combination with their hydrophobicity, hinder water penetration to affect dissolution.

No significant interaction was observed between any of the independent variables in release rate at 4 min.

Dissolution efficiency (DE_{30min}) values of the evaluated formulations are shown in Table 1. *P*-value of the applied model (<0.05) suggested the significance of the quadratic model for statistical evaluation. However the lack of fit test was significant for all models table and hence no model can adequately fits our data (Table 2).

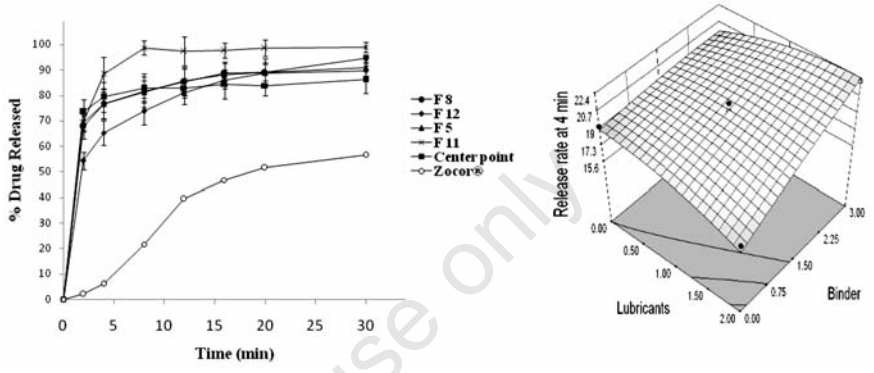

Figure 1. Effect of lubricant concentration (X_2) and binder concentration (X_3) on the dissolution profile of simvastatin from the prepared orodispersible tablets at constant superdisintegrant concentration (X_1), (Mean±SD).

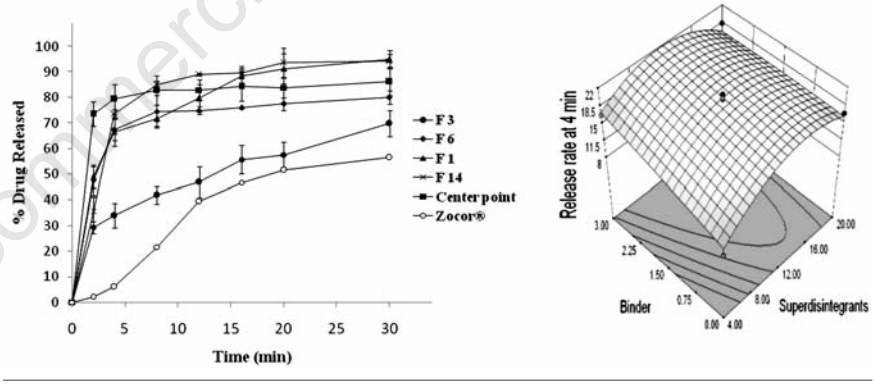

Figure 2. Effect of superdisintegrant concentration (X_1) and binder concentration (X_3) on the dissolution profile of simvastatin from the prepared orodispersible tablets at constant lubricants concentration (X_2), (Mean±SD).

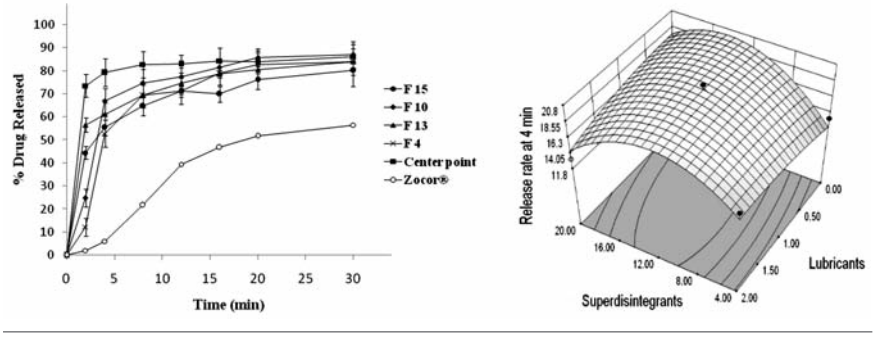

Figure 3. Effect of superdisintegrant concentration (X_1) and lubricants concentration (X_2) on the dissolution profile of simvastatin from the prepared orodispersible tablets at constant binder concentration (X_3), (Mean±SD).

Stability study

A stability indicating HPLC assay for determination of simvastatin in tablets was developed and validated. About 50 µL sample solution was injected into the HPLC and analyzed using an Ultrasphere ODS (250×4.6 mm) column (Beckman Coulter, USA) with UV detection at λ_{max}239 nm. The flow rate was maintained at 1.8 mL/min and the mobile phase consisted of 0.05M ammonium acetate: acetonitrile (40:60, v/v). Standard curves were linear over the concentration range of 10 µg /mL to 100 µg /mL. Intra-day and inter-day relative standard deviations ranged from 0.065-0.308% and 0.109-0.439% respectively (Table 5).

Tablet formulation number 11 consisting of 12% superdisintegrant, 2% lubricants and 3% binder was considered for stability study. It recorded the fastest dissolution (DR_{4min}=22.07) while keeping acceptable disintegration time and physical properties. The accelerated stability study of the selected formulation showed no significant changes in tablet hardness, friability, drug content (97.33-101.369%) and disintegration time. The similarity factor (f_2) values were equal to 92.13, 80.27 and 69.46 % after 1, 3 and 6 months, respectively indicating good similarity.

Conclusions

Simvastatin orodispersible tablets were successfully formulated by direct compression technique using the solid dispersion of the drug with Pluronic® F-68. They fulfilled the requirements of orodispersible tablets regarding fast disintegration and dissolution rate. This delivery system could be promising concerning increasing patient compliance and treatment convenience. Box-Behnken design was successfully used in evaluating the influence of different formulations variables on the prepared tablets.

Table 5 .Within day and day-to-day analytical precision.

Concentration (µg/mL)	Within-day* AUP (Mean±SD)	RSD %	Day-to-day° AUP (Mean±SD)	RSD %
10	872247.5±2538.513	0.291031	872229.5±2513.058	0.288119
20	1754467±1775.192	0.101181	1758677±7729.031	0.43948
25	2271159±5565.637	0.245057	2271173±5545.485	0.244168
40	3579505±5595.336	0.156316	3568978±9291.737	0.260347
50	4439036±6872.724	0.154825	4438159±5631.398	0.126886
75	6589379±20313.41	0.308275	6609182±7692.261	0.116387
90	7889374±5132.181	0.065052	7879211±9240.471	0.117277
100	8725472±1071.267	0.012277	8717954±9561.498	0.109676
Slope	87824.5±16.26346	0.018518	87805±43.84062	0.04993
R^2	0.999		0.999	

*Analyzed on the same day. °Analyzed on seven different days. RSD, relative standard deviation.

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