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Design of Experiments for Tablet Compression of Valsartan and Pravastatin Fixed-Dose Combination Tablet

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Design of experiment is important to set-up of new manufacturing processes with the impact of the variables. The object of this study was to select the ranges of critical process parameters in the compression process of valsartan and pravastatin fixed-dose combination tablets by using design of experiment (2^3 full factorial design with three center points). 3-Factorial (compression force, press speed and feeder speed), 4-level (hardness, disintegration, content uniformity and dissolution) and 1-center (n = 3) points as critical quality attributes were applied for the design of experiment batch using Design Expert Software. Compression force was an important factor in the hardness, disintegration and dissolution results ($p < 0.05$), more so than press and feeder speeds. The results indicated that compression force (from 8 to 12 kN), press speed (from 15 to 25 rpm) and feeder speed (from 10 to 30 rpm) for tablet compression were ideal ranges of operation for the critical process parameters.

Keywords: Valsartan, Pravastatin, Quality by design, Design of experiment, Tablet compression.

INTRODUCTION

Valsartan is a nonpeptidergic angiotensin II type 1 receptor antagonist, similar to other sartans [1,2]. It is absorbed rapidly, with a peak plasma level at about 3 h and plasma half-life of about 7.5 h after oral administration [3]. The low bioavailability of valsartan (25 %) may be caused by poor solubility in acidic pH conditions [4]. Valsartan is also used in combination with diuretic drugs, such as hydrochlorothiazide, which is effective in lowering blood pressure [1].

Pravastatin sodium, a 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase inhibitor, is a member of the statin family and used for treating hypercholesterolemia by reducing cholesterol biosynthesis [5]. It is also used in combination therapy, having beneficial effects on blood pressure [6]. The maximum plasma concentration of pravastatin occurs at approximately 0.88-1.00 h following oral administration, followed by a very low half-life at 1.97-2.15 h [7]. Pravastatin has a low bioavailability (18 %), due in part to extensive first-pass metabolism (about 70 %) [7].

In the quality-by-design approach to the tableting process in formulation development, an understanding of the tableting process is important for stable manufacturing on a commercial scale, as well as ensuring a robust-quality product, as described in the International Conference on Harmonization (ICH) Q8 (R^2) guideline [8]. All drug-manufacturing processes must consider how input material attributes and manufacturing process parameters can potentially affect the intermediate and finished product quality attributes. Critical process parameter, proven acceptable ranges and the design space of the manufacturing process are established in the design of experiment applications of the target formulation [8]. For the design of experiment application of tableting, critical process parameters affecting critical quality attributes are projected using project team knowledge and experience, such as operational parameters (including pre- and main compression, turret speed and feeder speed) and possible product outcome (including thickness, hardness, disintegration and dissolution) [9].

In this study, the effects of compression force, press speed and lubricant mixing time on the disintegration time, dissolution, content uniformity and hardness of a valsartan and pravastatin fixed-dose combination (FDC) tablet were evaluated by a design of experiment approach. A three-factor, two-level (2^3) full factorial design with three center points was used and eleven experimental runs were performed. The object of this study was to optimize the valsartan and pravastatin fixed-dose combination tablet formulation by the design of experiment application of ingredients and critical process parameters pertaining to the drug product quality attributes.

EXPERIMENTAL

Valsartan was purchased from MSN Laboratories Private Limited (Hyderabad, India). Pravastatin was obtained from Hisun Pharmaceutical Co. Ltd. (Zhejiang, China). Microcrystalline cellulose (Vivapur types 101, JRS, Germany), magnesium oxide (Heavy, Tomita, Japan), low-substituted hydroxypropyl cellulose (LH22, Shinetsu, Japan), croscarmellose sodium (Acdisol, FMC biopolymer, Belgium), magnesium stearate (Hyqual, Mallinckrodt, USA) was used for formulation study. All other chemicals and reagents were of commercially available pharmaceutical grades. The reference drugs used were valsartan (Diovan®, Novartis Co. Ltd) and pravastatin (Mevalotin®, Daiichi Sankyo Co. Ltd).

Preparation of the valsartan and pravastatin fixed-dose combination tablet: First, an immediate-release fixed-dose combination tablet of valsartan and pravastatin was prepared using the wet granulation method. The tablet was composed of valsartan (160 mg), pravastatin (40 mg), microcrystalline cellulose (45 mg), magnesium oxide (5 mg) and low-substituted hydroxypropyl cellulose (40 mg). Drugs and excipients were prepared with 24 mg of distilled water in the shear mixer from Nara Machinery Co. Ltd (NMG-1L. Tokyo, Japan) for 10 min and then wet granules were passed through a 1.7 mm screen to crush agglomerates. Wet granules were spread on trays and dried in a tray-drying oven at 60 °C (O'Hara Technologies, Inc., Richmond Hill, Canada) until the loss on drying (LOD) was no more than 1.5 % w/w. The dried granules were sieved (Quadro Comil 197S, Quadro Engineering, Canada) with a 990 μm screen at 1,200 rpm. The superdisintegrant (croscamellose sodium, 45 mg) and lubricant (magnesium stearate, 5 mg) were added to the sieved granules and mixed by a double cone blender (HS-DCM-10, Hansung F&C Co., Korea) for 300 revolutions at 15 rpm. Tablets (target weight of 430 mg) were compressed under various conditions (8, 12 and 16 kN) using a Piccola Nova tablet press (BD 4+4, Buenos Aires, Argentina). As shown in Table-1, the initial risk assessments showed that dissolution, assay and content uniformity were at a medium and high risk of being affected by the tablet compression process, which is just one part of the overall manufacturing process. Table-2 summarizes the risk assessment of the effects of the tablet compression process variables (press speed, feeder speed and compression force), affecting quality attributes such as weight variability, hardness, content uniformity, disintegration and dissolution [9,10]. A three-factor, two-level (2^3), full factorial design with three center points was used and evaluated to see if any curvature effects exist. As shown in Table-3, eleven batch formulations (each 0.85 kg) were prepared and manufactured for design of experiment study. Design Expert Software, Version 9.0.5.1 (Stat-Ease Inc., Minneapolis, MN, USA) was used to investigate the relationship between the input material attributes and process parameters related to compression and the output drug product quality attributes.

Loss on drying: Moisture content by loss on drying was determined using a halogen moisture analyzer (HG63, Mettler Toledo GmbH, Greifensee, Switzerland) using 5 g of wet granules at 105 °C for 15 min.

Hardness: Tablet hardness was determined by diametrical compression using a tablet hardness tester (8 M, Dr. Schleuniger, Switzerland). The mean hardness of 6 tablets selected randomly from each batch was measured and reported.

Content uniformity: Content uniformity test results of individual tablets (n = 10) were analyzed by assay with pravastatin sodium tablets and valsartan tablets USP monograph (USP37-NF32).

TABLE 1
INITIAL RISK ASSESSMENT OF THE MANUFACTURING PROCESS FOR VALSARTAN AND PRAVASTATIN FIXED-DOSE COMBINATION TABLETS

Process step	Drug product critical quality attributes			
	Assay	Content uniformity	Dissolution	Degradation products
Mixing & Wet granulation	Low	Low	High	Low
Drying	Low	Low	Medium	Medium
Granulate screening	Low	Low	High	Low
Final blending	Low	Medium	Low	Low
Tablet compression	Medium	High	High	Medium

TABLE-2
DESIGN OF THE 2^3 FULL FACTORIAL DESIGN OF EXPERIMENT TO STUDY TABLET COMPRESSION PROCESS VARIABLES

Factors: Process parameter		Range and levels		
		-1	0	+1
A	Press speed (rpm)	15	20	25
B	Feeder speed (rpm)	10	20	30
C	Compression force (kN)	8	12	16
Responses		Goal	Acceptable ranges	
Y_1	Hardness (kP)	Define acceptable range	To be defined based on other responses	
Y_2	Tablet disintegration time (min)	Minimize	< 4 min	
Y_3	Content uniformity of valsartan (% RSD[a])	Minimize % RSD	< 2 %	
Y_4	Content uniformity of pravastatin (% RSD)	Minimize % RSD	< 2 %	
Y_5	Dissolution similarity of valsartan (f2)	Maximize	≥ 55 (f2)	
Y_6	Dissolution similarity of pravastatin (f2)	Maximize	≥ 55 (f2)	

[a]Relative standard deviation

TABLE-3
EXPERIMENTAL RESULTS OF THE 2^3 FULL FACTORIAL DESIGN OF EXPERIMENT TO STUDY MIXING AND TABLET COMPRESSION PROCESS VARIABLES

Batch No.	Factors: Process variables			Responses					
	A	B	C	Y_1	Y_2	Y_3	Y_4	Y_5	Y_6
1	20	20	12	8.55	798.74	0.91	1.11	66.89	70.22
2	20	20	12	8.99	211.35	1.04	1.45	67.44	69.87
3	15	30	8	5.88	173.55	1.25	1.31	65.12	66.59
4	15	30	16	12.14	250.12	1.33	1.52	53.11	51.78
5	25	10	16	11.89	260.74	1.54	1.65	52.88	51.93
6	25	10	8	6.17	170.15	1.44	1.66	66.22	69.71
7	20	20	12	9.12	223.87	1.11	1.23	65.12	71.45
8	25	30	8	5.91	175.44	1.57	1.68	68.77	68.45
9	15	10	8	6.21	175.14	1.22	1.42	67.23	69.44
10	15	10	16	11.57	261.47	1.32	1.55	51.79	53.74
11	25	30	16	10.11	262.97	1.65	1.78	52.74	52.91

A = Press speed (rpm); B = Feeder speed (rpm); C = Compression force (kN); Y_1 = Hardness (kP); Y_2 = Tablet disintegration time (s); Y_3 = Content uniformity of valsartan (% RSD[a]); Y_4 = Content uniformity of pravastatin (% RSD); Y_5 = Dissolution similarity of valsartan (f2); Y_6 = Dissolution similarity of pravastatin (f2).
[a]relative standard deviation

Disintegration test: The disintegration time for the valsartan and pravastatin fixed-dose combination tablet (n = 6) was evaluated using a single-unit disintegration test apparatus (DIT-200, Labfine, Korea).

Dissolution study: Dissolution testing of the tablets (eight individual tablets from each batch) was performed using USP dissolution apparatus 2 (the paddle method) in 1,000 mL of water at 50 rpm and 37 ± 0.5 °C for 60 min. Aliquots (5 mL) were withdrawn at specific sampling time points (5, 10, 15, 30, 45 and 60 min) and filtered using a filtering rod (0.45 μm). The samples were analyzed using an HPLC (Agilent Technologies, 1200 series, USA) column (Phenomenex Synergi Polar RP, 150 mm × 4.6 mm, 4 μm). Peaks were detected at 230 nm with a UV detector (1200 series, Photo-Diode Array UV/visible detector, Agilent Technologies, USA).

RESULTS AND DISCUSSION

Preliminary study evaluation: Valsartan and pravastatin fixed-dose combination tablets were manufactured by the following process: wet granulation, drying, sieving, blending and tableting. The wet granulation method was selected owing to the poor flowability of valsartan and pravastatin and the reliability in process variable management compared to that associated with direct compression and dry granulation. In the design of experimental approach for wet granulation (0.85 kg lab-scale, the same volume as in the case of the tablet compression process design of experiment study), 40 to 60 g of granulating water (main factor for wet granulation) was optimal for the tablet with granulating time (from 6 to 10 min) and agitator speed (from 150 to 250 rpm). When hardness of 6-8 kP was achieved (main compression force of 12 kN, press speed of 20 rpm and feeder speed of 20 rpm), good blend uniformity, uniformity of dosage unit and assay was exhibited. Accordingly, the range of the tablet compression process was performed using this main compression force, press speed and feeder speed for the design of experiment study.

Evaluation of the tablet compression process: The quality target product profile (QTPP), a prospective summary of the quality characteristics of a drug product, is an essential element of a quality-by-design approach. An acceptable range of the critical quality attributes having physical, chemical and biological properties of the desired product quality from the quality target product profile (QTPP), based on the severity of harm to a patient, should be identified [8]. Formulation and process variables, such as all of the attributes of the input materials and apparatus affecting the quality of each process step, have the potential to impact critical quality attributes [11].

We have previously studied, the formulation and tablet compression processes, which are part of the whole manufacturing process. In this study, the suitability of the critical parameters of the tablet compression process (press speed, feeder speed and compression force) of valsartan and pravastatin fixed-dose combination tablet manufacturing was confirmed by eleven 0.85 kg lab-scale studies. The main compression force, turret speed and pre-compression force in the tablet compression process are important because they affect tablet hardness, disintegration time, friability, weight variation, content uniformity and dissolution [12]. An increase in feeder speed may also cause over-lubrication, which can affect assay, content uniformity and dissolution by inconsistent die filling [8]. Accordingly, the parameters for the tablet compression process constituted the focus of the design of experiment because they can affect the product critical quality attributes of assay, dissolution, content uniformity and disintegration time. Although the pre-compression force variable in the tableting process was excluded from this study because it was not observed in the formulation study, our study has shown that it may also impact capping caused by air.

The associated risk of the tablet compression process variables for the design of experiment study was evaluated as low to high based on feasibility studies and past experience [13]. The high risk in the compression process of valsartan and pravastatin fixed-dose combination tablets led us to select press speed, feeder speed and compression force affecting hardness, disintegration time, content uniformity and dissolution as responses or critical quality attributes (Tables 2 and 3). The manufacturing process was studied with controlled moisture and temperature, owing to the possibility of lactonization and oxidation of pravastatin [14,15].

The experimental results for the variables and responses are presented in Table-3. The results showed that the hardness varied from 5.88 to 12.14 kP, disintegration time from 170.15 to 262.97 sec, content uniformity of valsartan and pravastatin from 0.91 and 1.11 % to 1.65 and 1.78 %, respectively and dissolution (f2) of valsartan and pravastatin from 51.79 and 51.78 to 68.77 and 71.45, respectively. The compression force of the selected three independent factors was affected in the quality attributes of hardness, disintegration time and dissolution with slight variation.

As shown in the half-normal plot (Fig. 1a), compression force (effect = 5.39) is a more significant factor than feeder speed (effect ≤ 1.0) and press speed (effect ≤ 1.0) affecting hardness (kP) in the tablet compression process. The feeder speed and press speed values could show the normally distributed population as pure error based on Shapiro-Wilk test results. This is also shown compression force effect more clearly in the main effect plot (Fig. 2a). As shown in the analysis of variance (ANOVA) results for the design space of the adjusted model including center points in Table-4, the most significant factor affecting tablet hardness was compression force in the tablet compression process, reflecting the results of a previous study [12]. Tablet hardness increased with increasing compression force (positive effect), regardless of feeder speed and press speed (negative effects). The selected model (Table-4) indicated that the effect of compression force ($p \leq 0.0001$)

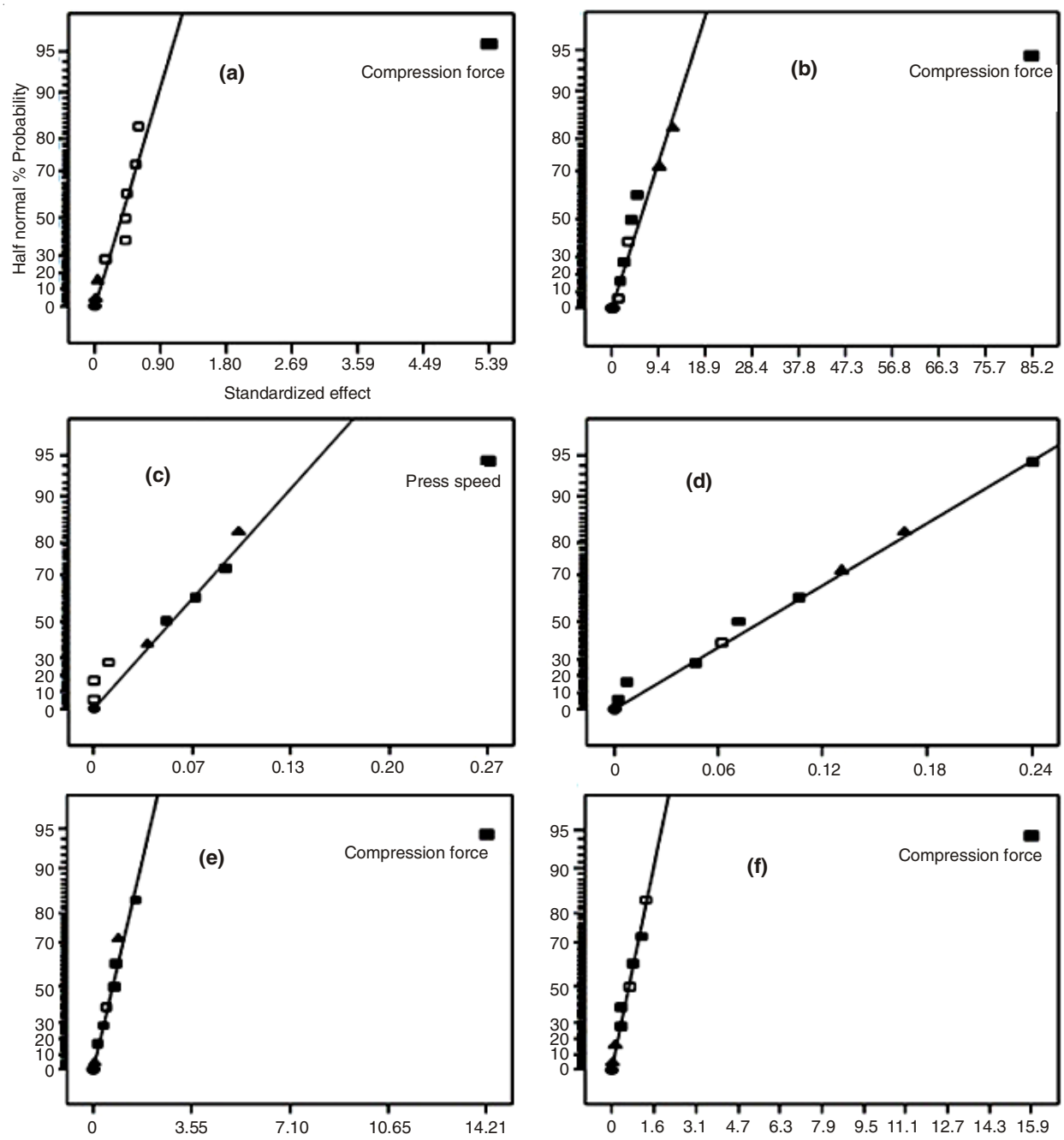

Fig. 1. Half-normal plots of the process variable effect on dissolution (a) Hardness, (b) Disintegration, (c) Content uniformity of valsartan, (d) Content uniformity of pravastatin, (e) Dissolution similarity of valsartan, (f) Dissolution similarity of pravastatin. ■ Positive effect, □ Negative effect, ▲ Error estimates

TABLE-4
ANOVA RESULTS OF THE SELECTED FACTORIAL MODEL

Source	Sum of squares	Degrees of freedom	Mean square	F-Value	*p*-Value (Probe > F)	Regression coefficient
Hardness						
Model	58.00	1	58.00	169.06	< 0.0001	0.9540
Lack of fit	2.57	6	0.43	4.79	0.1827	–
Disintegration time						
Model	14536.83	1	14536.83	266.10	< 0.0001	0.9675
Lack of fit	121.28	6	20.21	0.13	0.9786	–
Content uniformity of valsartan						
Model	0.15	1	0.15	3.35	0.1006	0.2710
Lack of fit	0.37	7	0.053	5.15	0.1721	–
Content uniformity of pravastatin						
Model	0.12	1	0.12	3.39	0.0988	0.2735
Lack of fit	0.25	7	0.036	1.22	0.5224	–
Dissolution similarity of valsartan						
Model	403.56	1	403.56	289.05	< 0.0001	0.7849
Lack of fit	8.23	6	1.37	0.93	0.5999	–
Dissolution similarity of pravastatin						
Model	509.28	1	509.28	412.24	< 0.0001	0.6930
Lack of fit	8.51	6	1.42	2.06	0.3625	–

on hardness of tablets is significant, with $p < 0.05$. In addition, lack of fit was not significant ($p = 0.1827$), showing that this is a good model for our adjustments [16].

Disintegration time was significantly influenced only by compression force (positive effect). The half-normal plot (Fig. 1b) and main effect plot (Fig. 2b) indicated that when compression force (effect = 85.26) increased from 8 to 16, disintegration time was found to increase regardless of feeder speed and press speed, owing to the increased hardness from more compaction. The disintegration time of batches 4, 5, 10 and 11 demonstrated unacceptable results (250.12-262.97 sec) based on the acceptance criteria (< 4 min). As shown in the ANOVA results of the adjusted model including center points in Table-4, the selected model was significant ($p \leq 0.0001$) and lack of fit was not significant ($p = 0.9786$). In general, when increased compression force was applied, tablets were harder and had a slower disintegration time as a result [17].

The effects of the three factors on content uniformity of pravastatin lie on the pure error line and were therefore not significant (Fig. 1d). The content uniformity of all batches had acceptable results, ranging from 1.11 to 1.78, within the acceptance criteria (% RSD < 2 %) (Table-3 and Fig. 2d). The p value of these results was more than 0.05 ($p = 0.0988$, Table-4). None of the process variables studied had a significant impact on the content uniformity of pravastatin. Although the effect of press speed (positive effect = 0.27) on the content uniformity of valsartan had acceptable results ranging from 0.91 to 1.65, the effect was only slightly significant (Fig. 1c, 2c and Table-3). However, the ANOVA results were not significant ($p = 0.1006$, Table-4). It was suggested that press speed in the tablet compression process is anticipated to be the most important factor on content uniformity, based on the ranking of importance parameters [9]. In this study, press speed was not found to affect the content uniformity for valsartan and pravastatin fixed-dose combination tablets.

The dissolution similarities of valsartan and pravastatin were significantly influenced by compression force (Fig. 1e and 1f). Main effect plots (Fig. 2e and 2f) indicated that when compression force (positive effect = 14.21 and 15.96 for valsartan and pravastatin) increased from 8 to 16, dissolution rate decreased with increased hardness and disintegration time. The dissolution similarity (f2) of batches 4, 5, 10 and 11 receiving 16 kN of compression force demonstrated unacceptable results (51.78-53.74), below the acceptance criteria (f2 ≥ 55) (Table-3). As shown in the ANOVA results of the adjusted model including center points in Table-4, the selected model was significant, with $p \leq 0.0001$ for valsartan and pravastatin. Moreover, lack of fit was not significant ($p = 0.5999$ and 0.3625

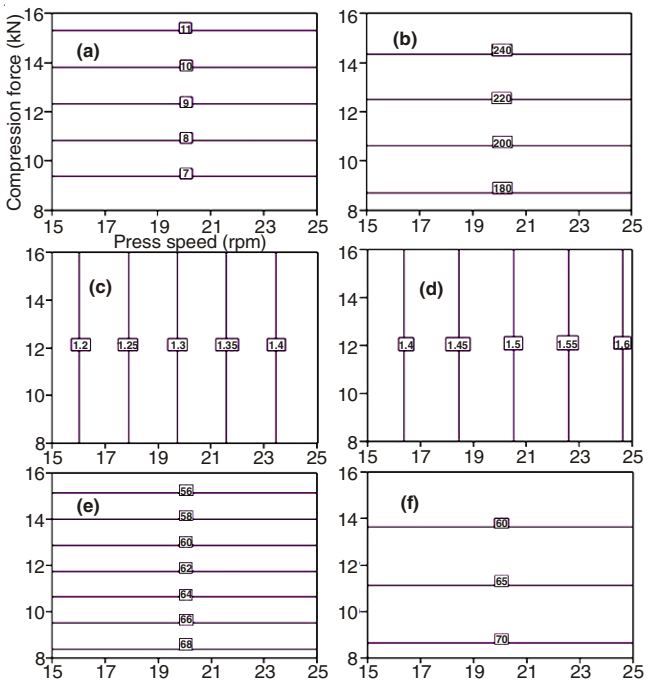

Fig. 2. Main effect of compression force and press speed on (a) Hardness, (b) Disintegration, (c) Content uniformity of valsartan, (d) Content uniformity of pravastatin, (e) Dissolution similarity of valsartan, (f) Dissolution similarity of pravastatin

for valsartan and pravastatin). In 2006, the Product Quality Research Institute [9] investigated whether compression force and press speed had an effect on dissolution. Optimum compaction pressures and press speed existed for acceptance criteria in dissolution as variable hardness and integration time results according to the pressure and speed values.

For the design space development, the difference and a ratio of predicted and adjusted regression coefficient (R^2) should beless than 0.2 and greater than 4, respectively [18]. Our results showed that the difference and ratio of the predicted and adjusted R^2 followed this rule at minimum (0.0069 and 4.03) and maximum (0.1711 and 27.126) values for all responses.

Development of design space: As shown in Fig. 3, resulting from a 95 % confidence interval (CI) on the mean values of responses, the design space was established in the region of black colour for the most successful operating ranges for the tablet compression process. The main compression force had the most significant impact on hardness, disintegration and dissolution, but not on content uniformity. Compression force (16 kN), regardless of press and feeder speeds, had unacceptable results for two responses (disintegration and dissolution). Although a high press speed had affected the content uniformity of valsartan, ANOVA results of the adjusted model included center points were not significant (Table-4). Accordingly, the ranges of the independent variables were well defined as press speed (15-25 rpm), feeder speed (10-30 rpm) and compression force (8-12 kN) had no significant impact on content uniformity, disintegration and dissolution. The point in the design space is not changed and can be built by the desired quality for the product.

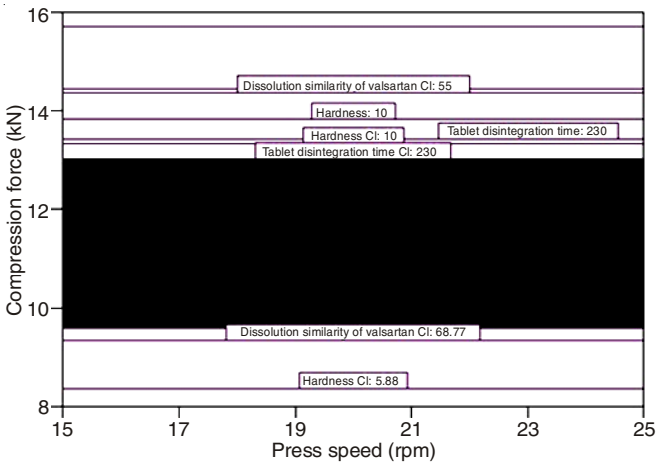

Fig. 3. Design space for the tablet compression process of valsartan and pravastatin fixed-dose combination tablet

Updated risk assessment and control strategy: The importance of the process parameters has to be evaluated by QTPP and critical quality attribute. The rating of several factors of the critical process parameters can be prioritized for risk management using Failure Mode and Effect Analysis (FMEAs) [19]. The risks identified during the initial assessment of the tablet compression process were reduced through the manufacturing process development study. These results have shown that the risk of factors that impact hardness, content uniformity, disintegration and dissolution was reduced from high to low as results of the design space were adjusted.

Control strategy is defined as ensuring the manufacture of a robust and defined product [20]. The operating range of the compression process for valsartan and pravastatin fixed-dose combination tablets is defined as the maximum and minimum limits that assure reproducibility [13]. The control strategy for the compression process of valsartan and pravastatin fixed-dose combination tablets should maintain the in-process tablet attributes of weight variation, hardness and disintegration within the required ranges, with thickness and friability excluded in this study. The target hardness required of tablets with the desired disintegration and dissolution is well established for all batches in design of experiment.

Conclusion

Compression force in the tablet compression process for design of experiment was selected as an important factor in formulation development. We identified that disintegration and dissolution were highly affected by compression force as a positive effect in lab-scale. Based on the results of the design of experiment study in lab-scale, the factor and process variables for the tablet compression process should be set and optimized within the acceptance criteria for scale-up.

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