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Original Article

Optimization of Pitavastatin Calcium and Micronized Fenofibrate Bi-layer Tablets Using Quality by Design

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ABSTRACT

Background and Purpose: This study aimed to develop bilayer tablets containing pitavastatin calcium and micronized fenofibrate. **Materials and Methods:** For optimization of manufacturing based on preliminary formulation research, a 2^4+3 full factorial Design of Experiments (DoE) study was conducted to elucidate the effects of four factors (Ludipress®, crospovidone, Polyethylene Glycol (PEG) 6000, main compression) influencing tablet Critical Quality Attributes (CQAs) such as hardness, friability, assay and dissolution rates at pH 1.2 and pH 4.5 with 2.88% Sodium Lauryl Sulfate (SLS). Analysis of variance was conducted using Design Expert software to evaluate the 4 responses (hardness, friability, assay and dissolution). **Results:** Ludipress®(p=0.0212), crospovidone (p<0.0001), PEG 6000 (p=0.0011) and main compression (p=0.0314) significantly affected friability. Hardness was also affected by crospovidone (p=0.0208). Dissolution rates at pH 4.5 with 2.88% SLS were affected by the interaction between crospovidone and PEG 6000 (p=0.0417). These results indicate that the optimized ranges of Ludipress® (4.55-10.59%), crospovidone (7.36-8.94%), PEG 6000 (8.06-9.09%) and main compression (1903-2158.41 kgf) had a positive influence on the tablet CQAs. **Conclusion:** Process optimization of the bilayer tablets was conducted using a four-factor, two-level, full-factorial design. This enabled the rapid evaluation and identification of critical process variables, facilitating the successful evaluation of bilayer tablets with excellent quality using the quality by design approach.

Keywords: Design of experiment, Micronized fenofibrate, Pita vastatin calcium, Quality by design.

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INTRODUCTION

Cardiovascular Disease (CVD) is a leading cause of mortality.[1] Dyslipidemia, an imbalance of lipids such as Triglycerides (TG), Low-Density Lipoprotein Cholesterol (LDL-C) and High-Density Lipoprotein Cholesterol (HDL-C), is a major risk factor for the onset of CVD.[1,2] To reduce the risk of CVD in patients with dyslipidemia, lifestyle modification and pharmacological therapies are necessary.[2]

Statins are the first-line treatment for dyslipidemia. These drugs reduce cholesterol synthesis by competitively inhibiting 3-methylglutaryl-coenzyme A reductase in the liver and reduce LDL-C and total cholesterol levels by increasing circulating LDL absorption in the blood through promoting LDL-C receptor expression in the same organ.[3] However, when statin monotherapy fails to achieve the desired treatment goal, combination therapy with fenofibrate can be used for enhanced cholesterol control.[4,5] Fenofibrate is a derivative of fibric acid. It stimulates the activity of Peroxisome Proliferator-Activated Receptor-Alpha (PPAR-α), which regulates the transcription of genes involved in lipid and cholesterol metabolism, thereby reducing blood levels of triglycerides and LDL-C while increasing HDL-C levels.[6]

Pitavastatin Calcium (PTC) is more effective at reducing blood LDL-C levels than other available statins and is more effective at increasing HDL-C levels than most other statins. Medications that affect the metabolism of statins can increase the risk of myopathy; however, PTC has been reported to have fewer drug-drug interactions than other statins because it is not significantly dependent on or affected by CYP enzymes.[7]

Fenofibrate is a lipid compound that is insoluble in water and has a low bioavailability of approximately 30%.[6,8] To improve its bioavailability, micronized fenofibrate has been developed. Micronization increases the exposed surface area to the solvent, thereby increasing the dissolution rate and enhancing bioavailability.[9] In the 1990s, Micronized Fenofibrate (MFF) was introduced, with improved bioavailability of approximately 30% compared to conventional fenofibrate.[6,8]

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Pellets containing active ingredients can be used to build multi-unit systems and can be filled into capsules or compressed into tablets.[10,11] Using tablet compression instead of filling capsules offers advantages such as higher industrial productivity and economic viability.[10] The Multiple-Unit Pellet System (MUPS) tablet form is widely used in solid dosage form design.[12] When MUPS dosage forms are taken orally, the small size of the multiple particles enables uniform distribution in the gastrointestinal tract, thereby improving bioavailability and reducing local drug concentration, which is more beneficial than the single-dose form.[10] This study aimed to develop MUPS tablets containing pelletized MFF and PTC layers.

Quality by Design (QbD) provides a systematic approach based on scientific and quality risk management principles for understanding and controlling products and processes rooted in predefined objectives. This enables the development of compositions and manufacturing processes that ensure predefined product specifications.[13] Key elements of QbD include the Quality Target Product Profile (QTPP), product and process design and understanding, scale-up, control strategies and continuous improvement, utilizing tools such as prior knowledge, risk assessment, Design of Experiments (DoE) and process analytical technology.[14] The DoE approach can be employed to understand the impact of composition factors/process variables, conducting efficient experiments by varying multiple factors simultaneously.[15] This study evaluated and optimized process variables of PTC and MFF bi-layer tablets using DoE for manufacture into a MUPS.

MATERIALS AND METHODS

Samples and Reagents

Bisron Cap® (Fenofibrate 200 mg) MFF pellets were supplied by Daewoo Pharmaceutical Co., Ltd (Busan, South Korea). PTC was supplied by MFC Co., Ltd. (Seoul, South Korea). Mannitol SD 100, Ludipress®, crospovidone, sodium stearyl fumarate, Low-Substituted Hydroxypropyl Cellulose (L-HPC) LH-11, magnesium aluminometasilicate and povidone K-30 were provided by Daewoo Pharmaceutical Co., Ltd. (Busan, South Korea). Polyethylene Glycol (PEG) 6000 was provided by Kolon Pharm (Daejeon, South Korea). Lactose monohydrate, hydrated ferric oxide and magnesium stearate were purchased from Whawon Pharm Co., Ltd. (Seoul, South Korea) and Masung and Co., Ltd. Sodium Lauryl Sulfate (SLS) was supplied by Tokyo Chemical Industry Co., Ltd. (Tokyo, Japan) and other chemicals, reagents and solutions were supplied by Samchun Chemical Co., Ltd. (Seoul, South Korea). Acetonitrile and methanol (Honeywell International Inc., North Carolina, USA) were of HPLC grade.

For the comparative dissolution test, the reference PTC and MFF bi-layer tablet was Uptava Cap® (pita vastatin calcium 2 mg, fenofibrate (micronized) 160 mg) from Daewon Pharmaceutical Co., Ltd.

Manufacture of PTC and MFF Bi-layer Tablets

The PTC layer (250 mg/tablet) was formulated by wet granulation and the MFF layer (400 mg/tablet) was manufactured by direct compression. The PTC layer was fixed in all the formulations. For all formulations, the MFF layer consisted of fixed MFF pellets (60.38%) and sodium stearyl fumarate (2.00%). Ludipress® (8-12%) and PEG 6000 (6-10%) were included in the DoE and the amount of mannitol was adjusted based on the ratio of these two excipients.

First, PTC was gradually blended with lactose monohydrate. L-HPC and magnesium aluminometasilicate were then added and mixed uniformly. Wet granulation was performed using distilled water containing dissolved povidone and hydrated ferric oxide. Wet granules were dried in a 70°C drying oven (OF-22GW, Jeio Tech, Daejeon, Korea) for 3 hr and the loss-on-drying was adjusted to 2.0% (w/w). Dried granules were sieved through a 500 μm screen and mixed with magnesium stearate. The MFF layer was prepared by mixing the MFF pellets with mannitol, Ludipress® and crospovidone. Then, 800 μm sieved PEG 6000 was blended into the mixture. Lastly, sodium stearyl fumarate was added and the mixture was blended to ensure granule lubrication. The final granules were compressed into a bilayer tablet using a single-punch tablet press (Autotab-200TR, Ichihashi Seiki Co., Ltd., Japan), with MFF as the first layer and PTC as the 2nd layer.

Risk Assessments and DoE

The initial risk assessment identified the risks associated with each factor of the product and manufacturing processes that could affect the Critical Quality Attributes (CQAs). Failure Mode and Effect Analysis was utilized and based on research experience and prior knowledge, the risk levels were classified as "low," "medium," or "high." Factors evaluated as high risk were Critical Material Attributes (CMAs) (Ludipress®, PEG 6000 and crospovidone) and Critical Process Parameters (CPP) (main compression) and a DoE study was conducted. The factors and response settings for the optimization studies are summarized in Table 1. DoE was conducted using Design Expert software version 13 (Stat-Ease Inc., USA). For the optimization studies, a $2^{4+}3$ Full Factorial Design (FFD) was applied, resulting in a total of 19 experiments (Table 2).

Hardness

The hardness of the tablets was determined using a hardness tester (Tablet Tester 8 M, Dr. Schleuniger® Pharma Tron, Ukraine), with an average value of three randomly selected tablets per batch being recorded.

Friability test

In the friability test, if the weight of each tablet is 650 mg or less, a quantity as close to 6.5 g as possible is selected for testing. After accurately weighing the tablets, they were subjected to 100

rotations at 25 rpm using a friability tester (FR-2000; Copley Scientific Limited, Nottingham, UK). Subsequently, the tablets were weighed again and friability was determined using the following formula:

$$Friability\ (\%) = \frac{(W_I - W_F)}{W_I} \times 100$$

W_I is the initial weight of the tablet and W_F is the final weight of the tablet after the friability test.

Estimation of Drug Content

The assay should be assessed using random units to ensure the consistency of the active ingredient across the manufactured dosage forms. The assay of PTC and MFF was to be in the range of 95-105%.

The sample content was evaluated using an Agilent 1100 Series HPLC system (Agilent Technologies, CA, USA), with PTC and MFF analyzed at wavelengths of 250 and 286 nm, respectively. The mobile phase consisted of a mixture of KH_2PO_4 buffer and methanol (25:75, v/v), with the buffer pH adjusted to 3.0 using phosphoric acid prior to mixing.

A standard stock solution of PTC was prepared as follows: PTC reference substance (22.05 mg) was weighed into a 50 mL volumetric flask and dissolved using acetonitrile 80% (acetonitrile and water, 80:20, v/v) by filling the flask to the mark. The PTC standard solution was prepared by transferring 5 mL of the standard stock solution into a 50 mL volumetric flask and then filling it up to the 50 mL mark with acetonitrile 80% (acetonitrile and water, 80:20, v/v). Subsequently, the solution was filtered through a 0.45 µM RC filter (Sartorius AG, Goettingen, Germany).

The method for preparing the standard solution of MFF was as follows: MFF reference substance (22.05 mg) was placed in a 100 mL volumetric flask and dissolved using acetonitrile 80% (acetonitrile and water, 80:20, v/v) by filling the flask to the mark and stirring at 500 rpm for 30 min. Subsequently, the mixture was filtered through a 0.45 µm RC filter (Sartorius AG, Goettingen, Germany).

The method for preparing the standard solution of PTC and MFF was as follows: one tablet was placed in a 100 mL volumetric flask and dissolved using acetonitrile 80% (acetonitrile and water, 80:20, v/v) by filling the flask to the mark and stirring at 500 rpm for 30 min. Subsequently, the resultant mixture was filtered through a 0.45 µM RC filter (Sartorius AG, Goettingen, Germany).

In vitro Dissolution Test

The dissolution test of the tablets was conducted using the paddle method (USP apparatus 2, 50 rpm) in pH 4.5 buffer solution containing 2.88% SLS (900 mL, 37±0.5°C) using a dissolution apparatus (PTWS 1210, Pharma Test Apparatebau AG, Hainburg, Germany). Dissolution samples were withdrawn at specified time points (10, 15, 30 and 45 min) and analyzed using the aforementioned HPLC system.

Data Analysis

All statistical analyses were conducted using Design Expert software version 13.0.5.0 (Stat-Ease Inc., Minneapolis, MN, USA). The contour lines and Design Space (DS) were evaluated to derive the optimal range. Analysis of Variance (ANOVA) was performed to determine the significance and main effect factors of the model.

Table 1: Initial risk assessment of tablet compression process variables.

Factors: Process Parameters			Range and Levels		
			-1	0	+1
CMAs	X_1	Ludipress (%)	8	12	16
	X_2	Polyethylene glycol (%)	6	8	10
	X_3	Crospovidone (%)	8	10	12
CPP	X_4	Main compression (kgf)	1800	2000	2200

Responses		Goal	Acceptable ranges
Y_1	Hardness (kp)	In range	$7.0 \le Y_1 \le 15.0$
Y_2	Friability (%)	Minimize	$Y_2 \le 1.0$
Y_3	Assay of Pitavastatin (%,w/v)	In range	$95.0 \le Y_3 \le 105.0$
Y_4	Assay of Fenofibrate (%,w/v)	In range	$95.0 \le Y_4 \le 105.0$
Y_5	Dissolution rate of Pitavastatin at pH 1.2 (%).	Maximize	$Y_8 \ge 85\%$ at 15 min
Y_6	Dissolution rate of Pitavastatin at pH 4.5 SLS (%).	Maximize	$Y_9 \ge 85\%$ at 15 min
Y_7	Dissolution similarity of Fenofibrate at pH 4.5 SLS (%).	Maximize	f2 value at pH 4.5 SLS $Y_9 \ge 50$ at 10, 15, 30, 45min

RESULTS

Initial Risk Assessment

The risk associated with each factor of the product and manufacturing processes that could impact the CQAs was identified through an initial risk assessment. The initial risk assessment classified the risk level based on research experience and prior knowledge as "low", "medium", or "high" and the results are summarized in Table 3. The pellets in the MUPS formulation must not have their coating damaged during compression and should rapidly disintegrate into individual pellets in the gastrointestinal fluid. In addition, the compression process should not affect drug release.[16] Therefore, the ratio of Ludipress® to PEG, excipients which act as fillers for the pellets, is important. Ludipress® is a coprocessing excipient with medium porosity and excellent flow properties. The residual porosity of Ludipress® allows sufficient water penetration for the rapid disintegration of compressed tablets, which may affect the release rate.[17] Therefore, it was assessed as "high". PEG 6000 improves flexibility and reduces tablet brittleness.[18] This can protect the coating film of the pellet from damage, but it can also reduce porosity and have a marked impact on the dissolution rate, thus it was evaluated as "high". Crospovidone particles is coarse and highly porous. This can lead to a significant increase in water absorption, which in turn significantly impacts the dissolution rate,[19] hence it was evaluated as "high".

DoE for Formulation Optimization

Four factors were selected through an initial risk assessment and a DoE study was conducted using a 2^4+3 FFD design. Each factor was set at three levels (-1, 0, 1) and 19 runs, including three center points, were tested. The results for each batch are summarized in Table 2. Hardness was evaluated in the range of 4.8-8.7 kp and friability was observed in the range of 0.06-1.2%. For analysis tests, PTC (%) ranged from 99.13-103.28, while MFF (%) ranged from 98.21-102.27. These results were within acceptable limits. The PTC (%) 15-min dissolution rates were 85.45-100.05% at pH 1.2 and 90.02-99.64% at pH 4.5, which fell within acceptable ranges. For MFF, the f2 values ranged from 33.63-54.84 at 2.88% SLS pH 4.5, with some batches exceeding the acceptable range.

ANOVA, DS and Updated Risk Assessment

Table 2 confirms the consistency of the results at the center points (batches 3, 14 and 19), indicating the reliability of the DoE outcomes. In ANOVA, a model was considered significant if the *p*-value was less than 0.05 and a lack of fit was considered significant if the *p*-value was greater than 0.05. Table 4 presents the results of the ANOVA (A-Ludipress®, B-crospovidone, C-PEG

Table 2: Results of DoE experiment of 2^4+3 FFD to optimize manufacturing process.

Batch No.	Factors				Responses						
	X_1 (%)	X_2 (%)	X_3 (%)	X_3 (kgf)	Y_1 (kp)	Y_2 (%)	Y_3 (%)	Y_4 (%)	Y_5 (%)	Y_6 (%)	Y_7 (-)
1	16	10	8	1800	6.0	0.68	101.58	102.27	93.12	96.81	47.51
2	8	6	12	1800	7.3	0.21	99.13	100.77	100.05	98.09	45.70
3	12	8	10	2000	8.8	0.16	101.04	101.35	92.75	98.23	51.79
4	16	6	12	1800	7.9	0.11	103.24	99.13	96.96	97.61	42.87
5	16	6	8	1800	7.1	0.13	102.32	98.32	94.14	98.83	45.83
6	8	6	8	2200	7.7	0.12	101.76	101.18	93.89	96.92	52.34
7	16	6	8	2200	7.9	0.08	102.39	98.77	96.06	97.60	42.35
8	16	10	8	2200	6.3	0.47	101.82	99.27	95.24	99.64	53.28
9	16	6	12	2200	8.6	0.06	101.13	98.35	93.01	91.65	37.67
10	8	10	12	1800	6.1	0.48	100.94	99.2	94.77	98.48	54.84
11	16	10	12	1800	6.6	0.37	100.87	100.06	96.84	98.64	42.85
12	16	10	12	2200	7.4	0.13	100.34	99.61	95.57	99.16	56.47
13	8	10	8	1800	4.8	1.20	101.09	98.21	92.52	95.19	33.63
14	12	8	10	2000	8.2	0.17	102.04	100.85	92.05	98.06	51.30
15	8	10	8	2200	5.9	1.00	100.05	99.13	95.84	96.47	44.57
16	8	10	12	2200	6.4	0.14	101.87	100.36	85.45	90.02	46.14
17	8	6	12	2200	7.5	0.09	103.28	98.32	87.51	94.61	36.98
18	8	6	8	1800	5.6	0.29	100.93	101.18	92.00	95.57	52.54
19	12	8	10	2000	8.7	0.17	100.83	99.85	93.01	98.66	51.91

Table 3: **Initial risk assessment of tablet compression process variables.**

Material and process variables	Drug product CQAs			
	Hardness	Friability	Assay	Dissolution
Mannitol SD 100	Low	Low	Low	Low
Ludipress	Medium	High	Low	Medium
Crospovidone	Medium	High	Low	High
Polyethylene glycol 6000	Medium	High	Low	High
Sodium Stearyl Fumarate	Low	Low	Low	Low
Lactose Monohydrate	Low	Low	Low	Low
Low-substituted Hydroxypropyl cellulose LH-11	Low	Low	Low	Low
Magnesium Aluminometasilicate	Low	Low	Low	Low
Povidone k-30	Low	Low	Low	Low
Hydrated Ferric Oxide	Low	Low	Low	Low
Magnesium stearate	Low	Low	Low	Low
Mixing and Wet Granulation	Low	Low	Low	Low
Drying and Screening	Low	Low	Low	Low
Final mixing and Lubricant	Low	Low	Low	Low
Pre-compression	Low	Low	Low	Low
Main compression	High	High	High	High

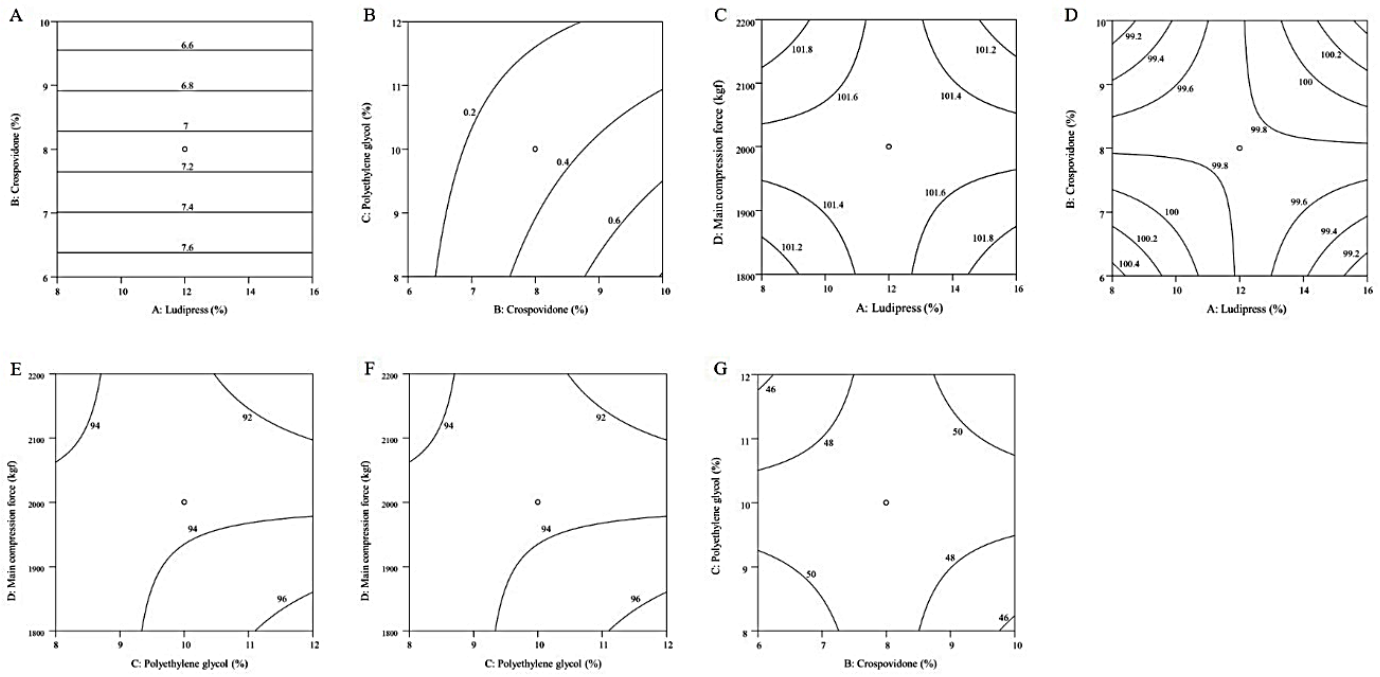

Figure 1: Main effect of ludipress, PEG 6000, crospovidone and main compression on (A) Hardness, (B) Friability, (C) PTC assay, (D) FFM assay, (E) pH 1.2 dissolution rate at 15 min of PTC (F) pH 1.2 dissolution rate at 15 min of PTC, (G) f2 value of pH 4.5 SLS FFM, ○; center points (*n*=3).

6000 and D-main compression) and Figure 1 shows a contour plot illustrating the primary influencing factors for each CQA.

In the hardness test, B-crospovidone (p=0.0208) was identified as the main factor (Figure 1A). Regarding friability, A-Ludipress® (p=0.0212), B-crospovidone (p<0.0001), C-PEG 6000 (p=0.0011) and D-main compression (p=0.0314) were identified as the main influencing factors, with an interaction observed between BC (p=0.0030) (Figure 1B). In the assay test, interactions were observed between various factors such as AD (p=0.0332), ABD (p=0.0416), ACD (p=0.0170) for PTC and AB (p=0.0016), ABC (p=0.0173), ABD (p=0.0185), BCD (p=0.0409) for MFF (Figure 1C, D). The dissolution test results showed that the dissolution rate of PTC at pH 1.2 (%) was influenced by A-Ludipress® (p=0.0295) and D-main compression (p=0.0384), with interactions between CD (p=0.0004) and ACD (p=0.0385) (Figure 1E). The dissolution rate of PTC in 2.88% SLS pH 4.5 (%) was influenced by the interaction between CD (p=0.0265) (Figure 1F). Additionally, the BC (p= 0.0417) interaction affected the dissolution similarity of MFF at pH 4.5 (%) (Figure 1G).

In this study, the values within the criteria for formulation optimization were confirmed. Figure 2 shows the DS; the white dot represents the center point repeated three times and the black area, including this point, satisfies all the quality attributes. Ludipress® ranged from 4.55% to 10.59%, crospovidone ranged from 7.36% to 8.94%, PEG 6000 ranged from 8.06% to 9.09% and main compression force ranged from 1903 kgf to 2158.41 kgf, all within the ranges deemed to satisfy all quality characteristics. Lastly, by optimizing the factors affecting the hardness, friability, assay and dissolution, the manufacturing process was updated from high-to low-risk.

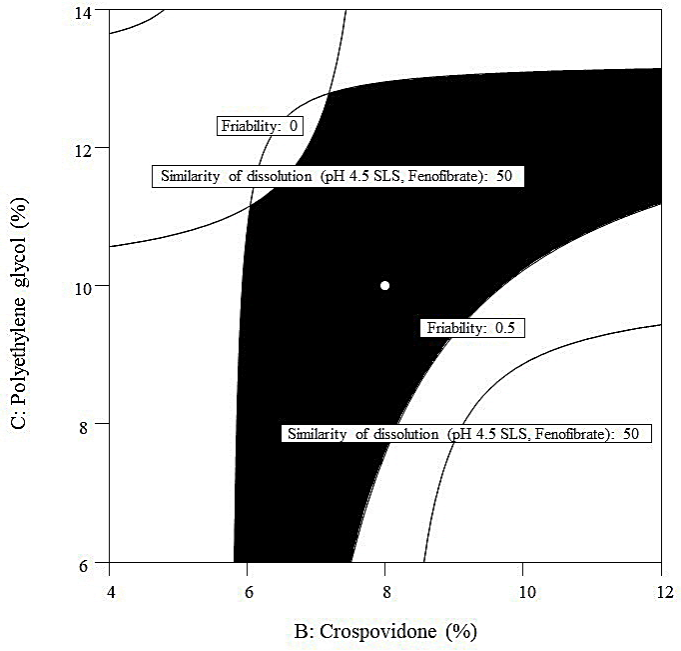

Figure 2: DS of the PTC and FFM bi-layer tablet depending on crospovidone and PEG. ○; center points (n=3).

DISCUSSION

The purpose of this study was to optimize a bilayer tablet formulation of PTC and MFF using DoE. DoE is a method used to determine the relationship between input and output variables using mathematical models, enabling the establishment of constrained control strategies.

The main factor influencing the hardness was B-crospovidone (p<0.0208). As shown in Figure 1A, the hardness decreased as the crospovidone content increased. Crospovidone has rough particles and high porosity, thus affecting hardness.[19]

The main factors affecting friability were A-Ludipress® (p=0.0212), B-crospovidone (p<0.0001), C-PEG 6000 (p=0.0011) and D-main compression (p=0.0314), with an interaction effect observed between BC (p=0.0030). As shown in Figure 1B, Ludipress® and crospovidone increased the residual porosity of the formulation, whereas PEG 6000 and a high compression force decreased the residual porosity, thus affecting the friability of the formulation. Ludipress® and crospovidone increased the residual porosity within the formulation, whereas PEG 6000 and a higher main compression force reduced residual porosity, thus affecting the friability of the formulation.[17-19]

Interactions were observed between AD (p=0.0332), ABD (p=0.0416) and ACD (p=0.0170) for PTC content and AB (p=0.0016), ABC (p=0.0173), ABD (p=0.0185) and BCD (p=0.0409) for MFF content. MUPS tablets may experience pellet separation in the tablet matrix due to the size and characteristics of the pellets, as well as the properties and particle size of the additives.[20] However, as depicted in Figure 1C and Figure 1D, all results for the PTC and MFF contents were within acceptable ranges and no significant changes were observed. The effects of these interactions were minimal.

At pH 1.2, the PTC dissolution rate was primarily affected by Ludipress® (p=0.0295) and main compression (p=0.0384), confirming an interaction between CD (p=0.0004) and ACD (p=0.0385). As Ludipress® increased, the internal porosity of the formulation increased, leading to an increase in dissolution rate, while an increase in main compression resulted in decreased internal porosity, leading to a decrease in dissolution rate.[17] However, as shown in Figure 1E, all results were within the acceptable range and no significant changes were observed. Therefore, the independent variables did not significantly affect the dissolution rate of PTC at pH 1.2.

Figure 1F confirms that the PTC dissolution rate at pH 4.5 with 2.88% SLS was influenced by the interaction of C and D; however, all results were within the acceptable range and there was no significant change. Therefore, the impact of the CD interaction on the dissolution rate of the PTC was minimal.

Table 4: ANOVA results of the 2^4+3 FFD.

Response	Source	Sum of Squares	d_f [a]	Mean Square	*p*-value	R^2
Hardness	Model	6.38	1	6.38	0.0208	0.7763
	B-Crospovidone	6.38	1	6.38	0.0208	
	Lack of Fit	16.54	15	1.10	0.0725	
Friability	Model	1.60	5	0.3196	< 0.0001	0.8572
	A-Ludipress	0.1406	1	0.1406	0.0212	
	B-Crospovidone	0.7140	1	0.7140	< 0.0001	
	C-PEG 6000	0.3540	1	0.3540	0.0011	
	D-Main compression	0.1190	1	0.1190	0.0314	
	BC	0.2704	1	0.2704	0.0030	
	Lack of Fit	0.2662	11	0.242		
PTC assay	Model	10.41	3	3.47	0.0073	0.7407
	AD	3.24	1	3.24	0.0332	
	ABD	2.92	1	2.92	0.0416	
	ACD	4.24	1	4.24	0.0170	
	Lack of Fit	8.84	13	0.6800		
FFM assay	Model	17.85	4	4.46	0.0010	0.7121
	AB	7.83	1	7.83	0.0016	
	ABC	3.75	1	3.75	0.0173	
	ABD	3.66	1	3.66	0.0185	
	BCD	2.62	1	2.62	0.0409	
	Lack of Fit	6.55	12	0.5460		
Dissolution rate of Pitavastatin at pH 1.2 (%).	Model	144.54	4	36.13	0.0006	0.7308
	A-Ludipress	22.35	1	22.35	0.0295	
	D-Main compression	19.87	1	19.87	0.0384	
	CD	82.49	1	82.49	0.0004	
	ACD	19.82	1	19.82	0.0385	
	Lack of Fit	53.23	12	4.44		
Dissolution rate of Pitavastatin at 2.88% SLS pH 4.5 (%).	Model	29.19	1	29.19	0.0265	0.7578
	CD	29.19	1	29.19	0.0265	
	Lack of Fit	84.01	15	5.60		
Dissolution similarity of Fenofibrate at pH 4.5 SLS (%).	Model	163.52	1	163.52	0.0417	0.7220
	BC	163.52	1	163.52	0.0417	
	Lack of Fit	573.16	15	38.21		

[a] degrees of freedom.

At pH 4.5 with 2.88% SLS, a BC (p=0.0417) interaction was observed to influence the dissolution rate of MFF, with f2 values ranging from 33.63 to 54.84. Crospovidone is a superdisintegrant, utilizing both swelling and wicking mechanisms.[21] A polyethylene glycol film forms around PEG, coating drug substance particles and increasing the hydrophilicity of both the drug and the additive.[22] Consequently, the formulation expands rapidly upon water absorption from the medium, breaking down the tablet into smaller particles and increasing the surface area, leading to enhanced drug release from the dissolution medium.[21,23] The influence of the interaction of B and C on the f2 value of MFF at pH 4.5 with 2.88% SLS was clearly elucidated (Figure 1G).

Figure 2 depicts the DS for the development of the PTC and MFF bilayer tablets, indicating acceptable ranges for CQAs. Acceptance criteria satisfying all CQAs were as follows: Ludipress® ranging from 4.55% to 10.59%, crospovidone 7.36% to 8.94%,

polyethylene glycol 8.06% to 9.09% and main compression force 1903 kgf to 2158.41 kgf.

CONCLUSION

Process optimization of PTC and MFF bilayer tablets was conducted using a four-factor, two-level, full-factorial design. This allowed for the rapid evaluation and identification of critical process parameters that influenced the desired responses. In this study, the use of the QbD approach for process variables resulted in the successful evaluation of bilayer tablets of excellent quality.

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ABBREVIATIONS

PTC: Pitavastatin Calcium; **MFF:** Micronized Fenofibrate; **CPP:** Critical Process Parameters; **DoE:** Design of Experiments; **QTPP:** Quality Target Product Profile; **DS:** Design Space; **CQAs:** Critical Quality Attributes; **QbD:** Quality by Design; **CMAs:** Critical Material Attributes; **ANOVA:** Analysis of Variance; **FFD:** Full Factorial Design.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

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