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Original Research Article

Optimization of pitavastatin calcium and ezetimibe combination tablet using full factorial design

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Abstract

Purpose: *To identify the optimized region of formulation using quality by design for pitavastatin calcium (PTV) and ezetimibe (EZE) immediate-release fixed-dose combination tablets*
Methods: *Hardness, friability, disintegration time, content, content uniformity, and dissolution rate were critical quality attributes (CQAs). Through the initial risk assessment, microcrystalline cellulose (MCC), sodium starch glycolate (SSG), the amount of water in the wet granulation part, and the main compression force were identified to affect the CQAs, and a full factorial design of the experiment (DoE) was applied.*
Results: *Parameters in all the batches were significantly influenced based on the analysis of variance ($p < 0.05$). MCC affected content ($p = 0.0002$), content uniformity ($p = 0.0002$), and dissolution rate ($p = 0.0131$) while SSG affected friability ($p = 0.0004$), disintegration time ($p < 0.0001$), and dissolution rates (pH 4.5 for pravastatin: $p = 0.0227$, 0.5 % SLS (pH 4.5) for ezetimibe: $p < 0.0001$, and 0.5 % SLS (pH 6.8) for ezetimibe: $p = 0.0434$, respectively). The amount of water in wet granulation part and main compression were the main factors affecting hardness ($p = 0.0143$) and disintegration time ($p = 0.0005$). Optimized ranges included MCC (10 – 18 %), SSG (7.86 – 15 %), amount of water in the wet granulation part (38 – 43.52 %), and main compression (954 – 1133 kgf).*
Conclusion: *The optimized region ranges of MCC, SSG, compression force, and the amount of water in the wet granulation for manufacturing process development have been successfully achieved by the design of experiments (DoE) approach.*

Keywords: *Critical quality attribute, Design of experiment, Ezetimibe, Pitavastatin, Quality by design*

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INTRODUCTION

Pitavastatin calcium (PVT) was selected as the primary ingredient in this study due to its significantly low-density lipoprotein-cholesterol (LDL-C) lowering effect at low doses and minimal drug interactions among statins. With a pharmacokinetic profile of 80 % oral absorption, 60 % bioavailability, and a half-life of 8 – 9 h after a single dose, PTV is suitable for once-daily administration [1]. Based on its metabolic stability, PTV is effective for patients with hypertension and diabetes requiring additional treatment [2]. As a result, PTV exerts a high LDL-C-lowering effect at low doses due to its low metabolism and pharmacokinetics.

Ezetimibe is administered in addition to statins when it is unable to lower the target LDL-C level. Ezetimibe inhibits cholesterol absorption in the intestine [3]. The Niemann Pick Cell 1 Like 1 (NPC1L1) protein in the small intestine prevents the reabsorption of endogenous cholesterol secreted into small intestine cells [4]. Combination therapy is safe and more effective than doubling the statin dose [5]. As a result, it permits the administration of lower statin dosages [3].

Quality by design (QbD) is a systematic strategy that applies knowledge and quality risk management to identify and manage potential risks during manufacturing processes [6]. Ensuring the quality of products and enabling continuous improvement is necessary. To achieve these goals, the values must be derived by combining the material attributes and process parameters of the product using statistical experimental tools [7]. First, the essential critical quality attribute (CQA) exerts an impact on the quality target product profile. Then, the critical material attribute (CMA) and critical process parameter (CPP) that may cause significant effects are selected [8]. Subsequently, the design space (DS) is determined after confirming the range of influence of each factor on the CQA using a design of experiment (DoE) approach.

In this study, a DoE was performed using a 2^4+3 full factorial design (FFD), and the PTV and EZE IR fixed-dose combination tablets were optimized based on the derived DS.

EXPERIMENTAL

Samples and reagents

Pravastatin calcium was supplied by MFC Co, Ltd, Seoul, South Korea and EZE was supplied by NEULAND, Telangana, India. Lactose monohydrate, MCC (Avicel PH 101), sodium starch glycolate (SSG), magnesium aluminometasilicate, 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. Acetonitrile, methanol, and other chemicals, reagents, and solutions were purchased from Honeywell Burdick & Jackson, Muskegon, USA.

Manufacture of PTV and EZE IR fixed-dose combination tablet

The PTV and EZE IR fixed-dose combination tablets were formulated using the wet granulation method. First, PTV (2 mg/tablet) was mixed with magnesium aluminometasilicate, and this was followed by the addition of EZE (10 mg/tablet) and a small amount of lactose monohydrate. The remaining lactose monohydrate, MCC, SSG, and hydrated ferric oxide were added, mixed, and granulated using purified water. The wet granules were dried in a 70 ℃ dry oven (OF-22GW, Jeio Tech, Daejeon, Korea) for 1 h to adjust loss-on-drying to 1.5 – 2.0 % (w/w), and they were identified using a halogen moisture analyzer (MB90, Ohaus, Seoul, South Korea). Then, the granules were sieved with a 600 µm screen. Finally, magnesium stearate was added for lubrication, and the tablets were compressed using a single-punch tablet machine (Autotab-200TR, Ichihashi Seiki Co., Japan).

In all formulations, MCC (10, 20, and 30 %) and SSG (5, 10, and 15 %) per DoE level were included, with lactose monohydrate adjusted for MCC changes. Magnesium aluminometasilicate (2 %), hydrated ferric oxide (0.03 %), and magnesium stearate (1 %) were used.

Risk assessment and DoE study

The initial RA utilized failure mode and effect analysis, defining the risk of material attributes and process parameters in the CQA based on a combination of probability and severity of harm [9]. Risk levels were set to "low," "medium," and "high."

DoE is a method in which the controllable input parameters of a process are systematically varied to observe how they affect a response [8]. A 2^4 + 3 FFD was employed using the Design Expert software version 13 (Stat-Ease Inc., USA). To determine the reproducibility of the experiment, three central points were added to the 16 experimental points, resulting in 19 experimental points.

In Table 1, the factors include MCC and SSG, which are CMA, the amount of water in the wet granulation part, and the main compression, which is CPP. The levels were -1, 0, and +1. MCC was 10, 20, and 30 %, SSG was 5, 10, and 15 %, the amounts of water in the wet granulation part were 38, 47.6, and 57.2 %, and the main compressions were 800, 1000, and 1200 kgf, respectively. Level 0 (the center point) was repeated three times. The responses comprised the CQAs (hardness, friability, disintegration time, content, content uniformity, and dissolution rate), and the acceptable ranges are summarized in Table 1.

Table 1 Factor levels and responses acceptable ranges of a 2^4 + 3 FFD for DoE

		Factor	Level		
			-1	0	**+1**
CMA	X_1	Microcrystalline cellulose (%)	10	20	30
	X_2	Sodium starch glycolate (%)	5	10	15
CPP	X_3	Amount of water (wet granulation part, %)	38	47.6	57.2
	X_4	Main compression (kgf)	800	1000	1200
	Response		**Goal**	**Acceptable range**	
Y_1	Hardness (kp)		In range	$3 \leq Y_1 \leq 10$	
Y_2	Friability (%)		Minimize	$Y_2 \leq 1.0$	
Y_3	Disintegration time (s)		Minimize	$Y_3 \leq 60$	
Y_4	Content of PTV (%)		In range	$95.0 \leq Y_4 \leq 105.0$	
Y_5	Content of EZE (%)		In range	$95.0 \leq Y_5 \leq 105.0$	
Y_6	Content uniformity of PTV (AV*)		Minimize	$Y_6 \leq 15$	
Y_7	Content uniformity of EZE (AV)		Minimize	$Y_7 \leq 15$	
Y_8	Dissolution rate at 15 min of PTV in pH 4.5 (%)		Maximize	$Y_8 \geq 85$	
Y_9	f2 value* of EZE in pH 4.5 with 0.5% SLS (f2 value)		Maximize	$Y_9 \geq 50$	
Y_{10}	Dissolution rate at 15 min of PTV in pH 6.8 with 0.5 SLS (%)		Maximize	$Y_{10} \geq 85$	
Y_{11}	f2 value of EZE in pH 6.8 with 0.5% SLS (f2 value)		Maximize	$Y_{11} \geq 50$	

* AV: Acceptance value
* f2 value: Similarity factor

Hardness

Hardness was measured using a hardness tester (Tablet Tester 8M, Dr. Schleuniger® Pharmatron, Ukraine) by randomly selecting three tablets.

Friability

Friability was tested using a friability tester (FR 2000; Copley, UK). Tablets were rotated at 25 rpm for 4 min and reweighed after the test. The friability percentage was determined using Eq 1.

Friability (%) = {(I-F)/I}100 …… (1)

Where I is the initial weight, and F is the final weight

Disintegration time

The disintegration tests were performed using a tester DIT 200 (Fine Scientific Ltd., Vaughan, Canada). The media was distilled water at 37 ± 2 ºC, and the time for each tablet to completely disintegrate was measured in seconds.

Estimation of drug content

For the sample solution of PTV and EZE, a tablet was placed in a flask and filled to 50 mL with a 2:8 mixture of 0.05 M sodium acetate buffer and acetonitrile. The solution was stirred for approximately 30 min to allow dissolution. A content uniformity test was conducted for n = 10. If the acceptance value (AV) was 15 or less, content uniformity was judged as secured. For high-performance liquid chromatography (HPLC) analysis, the mobile phase was 0.1 % phosphoric acid:acetonitrile: methanol (41:50:9), and HPLC analysis conditions were as follows: a) the column was Acclaim 120 C18 (5 µm, 4.6 × 250 mm); b) the flow rate was 1.0 mL/min; c) the analysis time was 10 min; d) the injection volume was 20 µL; e) detection included PTV-250 nm and EZE-231 nm.

***In vitro* dissolution study**

The dissolution test was performed in pH 4.5 containing 0.5 % SLS and pH 6.8 containing 0.5 % SLS dissolution media (900 mL, 37 ± 0.5 ℃) according to USP apparatus 2 guidelines (paddle method, 50 rpm). Dissolution samples were prepared by withdrawing 2 mL of each medium from the vessel at predetermined time points (10, 15, and 30 min).

Statistical analysis

Data were analyzed using Design Expert® Software Version 13 (Stat-Ease Inc., USA). An analysis of variance (ANOVA) was conducted to assess the significance of the model and the main factors. According to the ANOVA, a model was considered significant when the *p*-value was < 0.05, the lack of fit was > 0.05, and the coefficient of determination (R^2) was > 0.7. The optimal range was determined using contours and DS.

RESULTS

RA of the PTV and EZE IR fixed-dose combination tablet

To optimize the formulation composition and manufacturing process of the PTV and EZE IR fixed-dose combination tablets, an initial RA was performed based on prior knowledge (Table 2). The initial RA identified MCC, SSG (CMA), the amount of water used for wet granulation, and main compression (CPP) as high-risk factors affecting CQA.

Microcrystalline cellulose is a low-moisture-grade cellulose that affects tablet density and possesses low compressibility [10,11]. Moreover, it is water-insoluble. These properties affect hardness, friability, disintegration time, and dissolution rate [12]. Microcrystalline cellulose was rated "high" for friability and dissolution rate and "medium" for hardness and disintegration time (Table 2). In preliminary studies, SSG, a disintegrant that swells with water, was observed to shorten the disintegration time and increase the initial dissolution rate of PTV and EZE as the ratio increased [13]. Thus, the risk level for these responses was rated "high" in Table 2. In the preliminary study, less water in the wet granulation part shortened the disintegration time, and this was identified as "medium." The granule size and porosity depend upon the amount of water in the wet granulation process. Thus, content, content uniformity, and dissolution rate were rated "high," and hardness, friability, and disintegration time were "medium" in Table 2 [14]. Additionally, the main compression influences tablet properties such as hardness, friability, disintegration time, and dissolution rate by diminishing porosity [15]. The risk levels for these responses were classified as "high" (Table 2).

DoE for formulation optimization

The MCC, SSG, amount of water in wet granulation and main compression were selected as the four factors for a DoE study conducted using a 2^4+3 FFD. The compositions and results for each batch are summarized in Table 3, and the acceptance criteria are summarized in Table 1. Hardness (kp) and friability (%) were measured at a range of 3.33 to 6.26 and range of 0.03 to 0.22 (Table 3). As described in Table 3, the disintegration times (s) ranged from 20 to 106, and certain batches (Nos. 5, 6, 7, 8, 13, 14, 15, and 16) were outside the acceptance criteria. In the content, PTV (%) ranged from 96.52 to 100.54 %, and EZE (%) ranged from 96.21 to 101.15. Regarding content uniformity, AV of PTV was 0.71 to 3.57, and that of EZE was 0.6 to 3.53. The results of these four responses (Table 3) met the acceptance criteria.

In Table 3, the dissolution rate of PTV at 15 min of PTV at pH 4.5 ranged from 78 to 90.44 %, and the dissolution rates of the four batches (No. 5, 6, 17, and 18) were less than 85 %. The similarity factor (f2 value) of EZE in 0.5 % SLS (pH 4.5) ranged from 35.62 to 85.09 %, and five batches (No. 6, 9, 14, 16, 18) were less than 50. The dissolution rate of PTV at 15 min of PTV in 0.5 % SLS (pH 6.8) ranged from 79.31 to 93.95 %, and 11 batches met the acceptance criteria.

Table 2: Initial RA of PTV and EZE IR fixed-dose combination tablet

Material and process variable	Drug product CQAs					
	Hardness	***Friability***	***Disintegration***	***Content***	***Content uniformity***	***Dissolution***
Lactose Monohydrate	Low	Low	Low	Low	Low	Low
Microcrystalline cellulose	Medium	High	Medium	Low	Low	High
Sodium starch Glycolate	Low	Low	High	Low	Low	High
Magnesium aluminometasilicate	Low	Low	Low	Low	Low	Low
Hydrated ferric oxide	Low	Low	Low	Low	Low	Low
Magnesium stearate	Low	Low	Low	Low	Low	Low
The amount of water in wet granulation part	Medium	Medium	Medium	High	High	High
Drying & Screening	Low	Low	Low	Low	Low	Low
Pre-compression	Low	Low	Low	Low	Low	Low
Main compression	High	High	High	Low	Low	High

The f2 value of EZE in 0.5 % SLS (pH 6.8) ranged from 45.01 to 96.76, and one batch (No. 14) was outside the acceptance criteria, as the f2 value was less than 50.

ANOVA results

Eleven models demonstrated reliability [16]. Factors significantly affecting the CQAs were identified using ANOVA (Table 4). The 11 contour plots in Figure 1 indicate that the main factors significantly influenced each response. In the hardness test, the amount of water in wet granulation (p = 0.0143) and compression (p < 0.0001) were the main influencing factors (Table 4 and Figure 1 A). Regarding friability, SSG (p = 0.0004) was the main factor, with an interaction between the two CPPs (p = 0.0065; Table 4 and Figure 1 B). Regarding disintegration time, SSG (p < 0.0001), water amount in wet granulation (p < 0.0001), and main compression (p = 0.0005) were the main factors affecting the BC interaction (p = 0.0058; Table 4 and Figure 1 C). As presented in Table 4 and Figure 1 D, the MCC (p = 0.0013) and the amount of water in the wet granulation part (p < 0.0001) were the main factors in the PTV content. For the EZE content (Table 4 and Figure 1 E), SSG (p = 0.0004) was the main affecting factor, with an observed AC interaction (p = 0.0056). In terms of content uniformity (Table 4, Figures 1 F and G), the MCC (p = 0.0002, p = 0.0002) exerted a significant influence on both the PTV and EZE. Dissolution tests indicated that SSG (p = 0.0227) and main compression (p = 0.002) were the main affecting factors for PTV at 15 min at pH 4.5 (Figure 1 H) and pH 6.8 in 0.5 % SLS (Figure 1 J), with an observed ACD interaction (p = 0.0043, p = 0.0002). As presented in Table 4, SSG (p < 0.0001, p = 0.0434) was commonly determined as the main factor affecting the f2 value of EZE in 0.5 % SLS (pH 4.5; Figure 1 I) and 0.5 % SLS (pH 6.8; Figure 1 K), and MCC (p = 0.0131) affected the f2 value of EZE in 0.5 % SLS (pH 4.5; Figure 1 I).

Design Space and updated Risk Assessment

The DS was derived from the DoE study as represented in Figure 2. The white point is the center point (n = 3), and the black area indicates the optimized range that satisfies the CQAs within an acceptable range. The desirable ranges for the ratio of MCC (10 – 18 %), SSG (7.86 – 15 %), the amount of water in the wet granulation part (38 – 43.52 %), and the main compression (954 – 1133 kgf) were established as control strategies. This study optimized four factors affecting CQAs, thus updating the RA to low risk.

DISCUSSION

The manufacturing processes of PTV and EZE IR fixed-dose combination tablets were optimized using DoE. The optimal ranges of the factors were derived such that all CQA appeared within an acceptable range of output variables for control strategies.

ANOVA after the DoE in this study indicated that the hardness factor was significantly influenced by the amount of water in the wet granulation part (p = 0.0143) and by the main compression force (p < 0.0001). The contour plot also indicates increased hardness at higher levels of these factors (the amount of water and the main compression force). The amount of water in the wet granulation part enhances cohesion, whereas the main compression reduces porosity, ultimately resulting in higher hardness [17]. In the friability test, a higher SSG ratio (p = 0.0004) lowered friability, and the amount of water and main compression force in the factor interaction (p = 0.0065) was significant. In theory, a high MCC ratio may affect friability and hardness due to its small particle size and low moisture content, both of which affect compressibility and flowability [10-12]. However, the results in this study were purportedly within a narrow range and were not considered meaningful. According to the disintegration results, an increase in SSG (p < 0.0001) ratio and a decrease in the amount of water in the wet granulation part (p < 0.0001) shortened the disintegration time as indicated in the contour plot. According to the ANOVA results, main compression (p = 0.0005), SSG and the amount of water interaction in factors (p = 0.0058) impacted the disintegration time. SSG is a commonly used super-disintegrant**.** This causes fine gelation and disintegration during swelling [13].

The cohesion between the granule molecules declined, and the tablet disintegrated more rapidly when the water content was reduced. Additionally, increasing the main compression decreases the porosity and delays disintegration, as a porous system absorbs water and aids in rapid tablet absorption. Thus, reduced porosity leads to delayed disintegration [15,18]. For the content test, MCC (p = 0.0013) and amount of water in the wet granulation part (p < 0.0001) were the main factors affecting SSG (p = 0.0004) influenced PTV, and MCC and the amount of water interacted to influence the content of EZE.

Table 3: Factor values and results of the response for each batch of a 2^4 + 3 FFD

Batch No.	Factor (X)						Response (Y)								
	X_1: Microcrystalline cellulose	X_2: Sodium starch glycolate	X_3: Amount of water in wet granulation part	X_4: Main compression	Y_1: Hardness	Y_2: Friability	Y_3: Disintegration time	Y_4: Content of PTV	Y_5: Content of EZE	Y_6: Content uniformity of PTV	Y_7: Content uniformity of EZE	Y_8: Dissolution rate at 15 min of PTV in 4.5	Y_9: f2 value of EZE in pH 4.5 with 0.5% SLS	Y_{10}: Dissolution rate at 15 min of PTV in 6.8 with 0.5% SLS	Y_{11}: f2 value of EZE in pH 6.8 with 0.5% SLS
	(%)	(%)	(%)	(kgf)	(kp)	(%)	(sec)	(%)	(%)	(AV)	(AV)	(%)	(f2 value)	(%)	(f2 value)
1	10	5	38	800	3.33	0.15	38	97.28	97.85	2.5	2.2	78	52.18	84.81	51.61
2	30	5	38	800	3.88	0.18	36	96.77	96.21	0.94	0.92	87.26	52.88	82.07	53.83
3	10	15	38	800	3.64	0.16	20	96.52	100.1	0.71	0.68	85.07	85.09	82.62	78.9
4	30	15	38	800	3.88	0.03	24	96.87	98.25	1.15	1.12	90.44	66.7	79.31	73.11
5	10	5	57.2	800	4.22	0.17	92	99.83	97.92	2.22	2.19	89.34	44.01	84.94	52.3
6	30	5	57.2	800	5	0.05	89	100.8	97.54	1.66	1.63	86.56	35.62	89.45	57.19
7	10	15	57.2	800	3.78	0.05	62	98.06	97.95	2.48	2.45	89.24	82.37	85.55	76.19
8	30	15	57.2	800	3.61	0.09	64	100.54	100.24	0.88	0.6	89.54	67.77	87.82	73.47
9	10	5	38	1200	4.66	0.21	45	96.95	96.53	2.15	2.1	85.47	61.02	86.13	82.68
10	30	5	38	1200	5.58	0.08	41	98.67	97.61	0.79	0.75	83.7	44.09	90.1	96.76
11	10	15	38	1200	4.66	0.07	33	97.86	98.4	1.99	1.96	90.41	78.35	84.3	72.69
12	30	15	38	1200	5.41	0.04	30	97.91	97.9	0.78	0.74	83.2	62.01	93.95	68.11
13	10	5	57.2	1200	5.1	0.22	106	98.43	97	3.57	3.53	82.7	43.46	88.64	64.07
14	30	5	57.2	1200	6.05	0.1	99	100.53	98.08	1.47	1.43	86.26	36.63	83.66	45.01
15	10	15	57.2	1200	4.83	0.16	77	97.47	97.79	3.5	3.47	86.6	64.82	88.08	60.63
16	30	15	57.2	1200	6.26	0.08	73	100.46	101.15	0.89	0.86	89.21	59.63	87.09	80.58
17	20	10	47.6	1000	4.76	0.05	50	99.08	99.08	1.29	1.26	88.62	70.17	86.81	74.26
18	20	10	47.6	1000	4.69	0.03	48	99.1	99.02	1.52	1.48	89.22	73.97	85.37	67.58
19	20	10	47.6	1000	4.88	0.04	51	99.43	99.37	1.26	1.22	90.42	71.08	86.67	74.85

Table 4: ANOVA results of a 2^4+3 FFD

Source	Sum of squares	df	Mean square	F-value	*P*-value	R^2
Hardness						
Model	10.62	3	3.54	29.96	< 0.0001	0.8570
D- Main compression	7.85	1	7.85	66.49	< 0.0001	
C	0.9073	1	0.9073	7.68	0.0143	
Lack of fit	1.75	13	0.1349	14.61	0.0658	
Friability						
Model	0.0523	5	0.0105	17.61	< 0.0001	0.8801
B- Sodium starch glycolate	0.0144	1	0.0144	24.25	0.0004	
CD	0.0064	1	0.0064	10.78	0.0065	
Lack of fit	0.0069	10	0.0007	6.92	0.1327	
Disintegration time						
Model	12005.25	4	3001.31	156.53	< 0.0001	0.9781
B- Sodium starch glycolate	1660.56	1	1660.56	86.61	< 0.0001	
C	9751.56	1	9751.56	508.59	< 0.0001	
D- Main compression	390.06	1	390.06	20.34	0.0005	
BC	203.06	1	203.06	10.59	0.0058	
Lack of fit	268.43	12	21.98	9.42	0.0999	
Content of PTV						
Model	30.60	4	7.65	19.14	< 0.0001	0.8454
A- Microcrystalline cellulose	6.44	1	6.44	16.11	0.0013	
C	18.68	1	18.68	46.75	< 0.0001	
Lack of fit	5.52	12	0.4598	11.90	0.0801	
Content of EZE						
Model	21.55	4	5.39	10.71	0.0003	0.7537
B- Sodium starch glycolate	10.63	1	10.63	24.13	0.0004	
AC	5.36	1	5.36	10.66	0.0056	
Lack of fit	6.97	12	0.5808	16.58	0.0583	
Content uniformity of PTV						
Model	8.97	2	4.49	14.75	0.0002	0.7483
A- Microcrystalline cellulose	6.97	1	6.97	22.92	0.0002	
Lack of fit	4.83	14	0.3447	17.04	0.0568	
Content uniformity of EZE						
Model	8.95	2	4.48	14.53	0.0003	0.7449
A- Microcrystalline cellulose	6.93	1	6.93	22.49	0.0002	
Lack of fit	4.89	14	0.3493	17.82	0.0544	
Dissolution rate of PTV at 15 min in pH 4.5						
Model	102.32	2	51.16	8.72	0.0028	0.7214
B- Sodium starch glycolate	32.27	1	32.27	6.35	0.0227	
ACD	65.04	1	65.04	11.08	0.0043	
Lack of fit	92.24	14	6.59	7.84	0.1187	
f2 value of EZE in pH 4.5 with 0.5% SLS						
Model	3172.88	3	1057.63	18.11	< 0.0001	0.7836
B- Sodium starch glycolate	2421.87	1	2421.87	41.46	< 0.0001	
A- Microcrystalline cellulose	461.93	1	461.93	7.91	0.0131	
Lack of fit	868.34	13	66.80	16.97	0.0570	
Dissolution rate at 15 min of PTV in pH 6.8 with 0.5% SLS						
Model	148.07	3	49.36	17.10	< 0.0001	0.7738
D- Main compression	40.26	1	40.26	13.95	0.0020	
ACD	65.69	1	65.69	22.76	0.0002	
Lack of fit	42.03	13	3.23	5.13	0.1748	
f2 value of EZE in pH 6.8 with 0.5% SLS						
Model	1929.96	5	385.99	4.80	0.0105	0.7488
B- Sodium starch glycolate	402.30	1	402.30	5.01	0.0434	
Lack of fit	1012.26	11	92.02	5.64	0.1600	

C- Amount of water in wet granulation

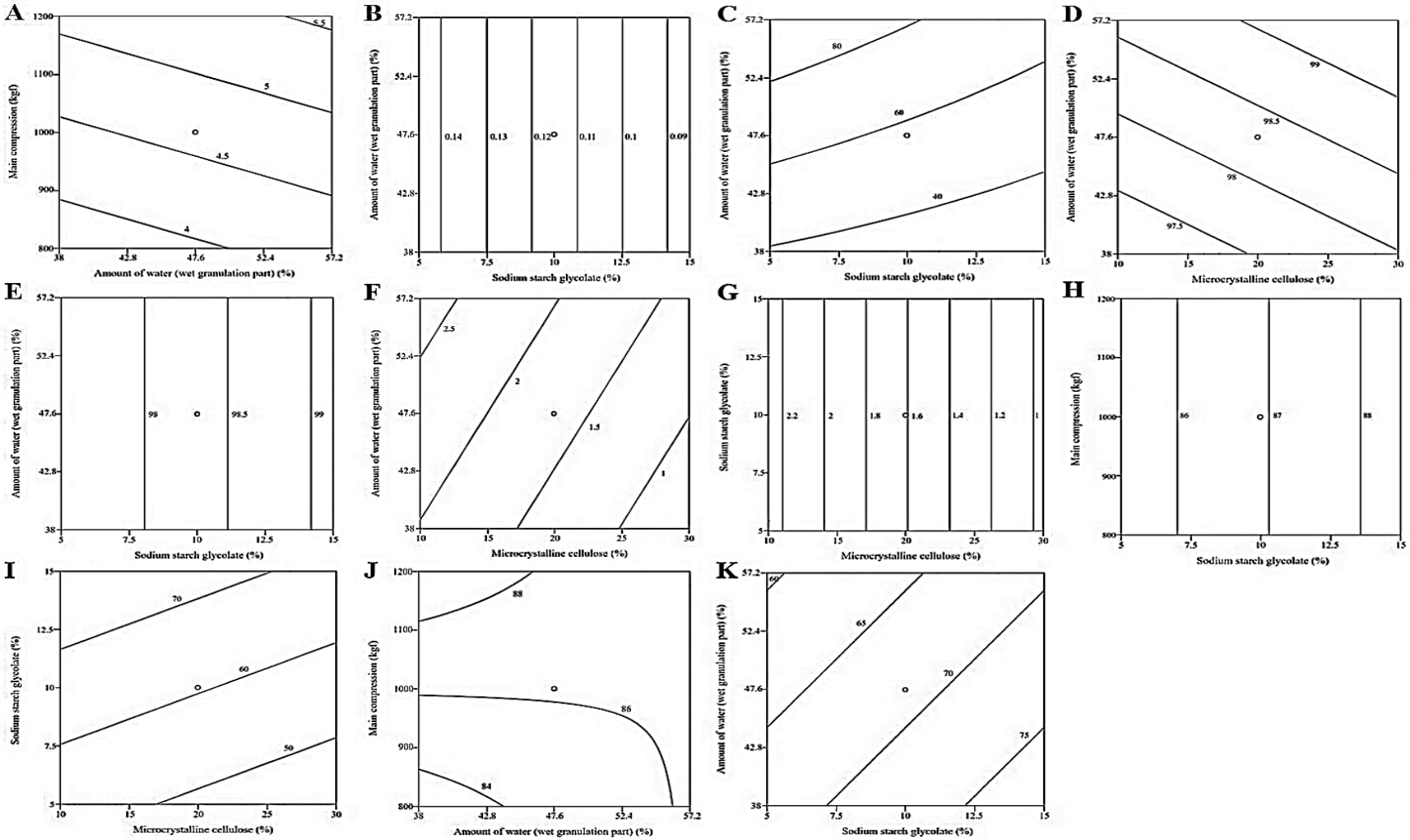

Figure 1: Main effect of MCC, SSG, the amount of water in wet granulation part, and min compression on (A) hardness, (B) friability, (C) disintegration time, (D) content of PTV, (E) content of EZE, (F) content uniformity of PTV, (G) content uniformity of EZE, (H) dissolution rate at 15 min of PTV in pH 4.5, (I) f2 value of EZE in pH 4.5 with 0.5 % SLS, (J) dissolution rate at 15 min of PTV in pH 6.8 with 0.5 % SLS, (K) f2 value of EZE in pH 6.8 with 0.5 % SLS. ○; center points (n = 3)

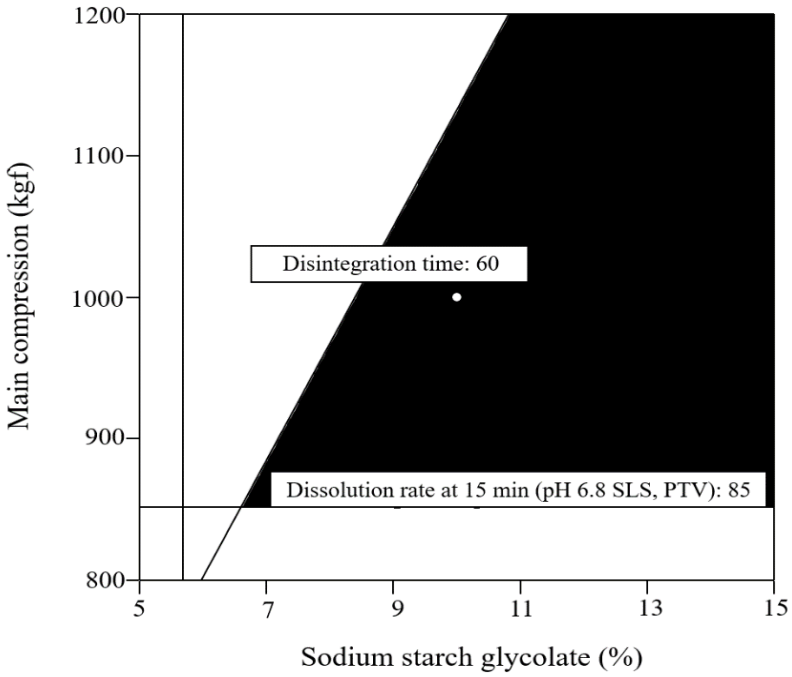

Figure 2: DS about the PTV and EZE IR fixed-dose combination tablet depending on SSG and main compression. ○; center points (n = 3)

Content uniformity and MCC (p = 0.0002) were the main factors. The granule size and moisture content vary depending on the amount of water in the wet granulation, and this may impact flowability [14]. Inappropriate mixing results in poor content uniformity. Additionally, MCC with small particle size and low moisture content results in poor flowability, and this affects content uniformity [11]. However, all response results were within the acceptable ranges. The ANOVA results also indicate that SSG (p = 0.0227) affected the dissolution rate at 15 min in the pH 4.5 for PTV, and the main compression (p = 0.0020) affected the pH 6.8 containing 0.5 % SLS. Additionally, the MCC, the amount of water, and the main compression force interaction (p = 0.0043) influenced the dissolution rate of the PTV. The contour plot indicates that a high ratio of SSG increased the initial dissolution rate of PTV at 15 min at pH 4.5. The amount of water in the wet granulation part lowered the dissolution rate at 15 min for PTV in the pH 6.8 solution containing 0.5 % SLS by increasing granule cohesion and preventing drug release [17]. For the dissolution rate of EZE, SSG was the main affecting factor. The MCC (p = 0.0131) also affected the f2 value of EZE in the pH 6.8 containing 0.5% SLS. Sodium starch glycolate is a disintegrant that swells in water and promotes disintegration. Therefore, it influenced the initial dissolution rate of [13]. Microcrystalline cellulose is a polymer that sinks and does not dissolve in water, and this interferes with drug release and contributes to the low f2 value of EZE.

CONCLUSION

The acceptable range of responses for CQAs (hardness, friability, disintegration time, content, content uniformity, and dissolution rate) in the DS for the development of the PTV and EZE IR-fixed-dose combination tablets has been shown in this study. The optimized region based on the effects of CMA and CPP on CQA was established based on MCC (10.0 – 18%), SSG (7.86 – 15 %), amount of water in the wet granulation part (38 – 43.52 %), and main compression (954 – 1133 kgf). Evaluation of the 11 responses within this range indicated that all met the acceptance criteria. These findings are expected to form the basis for further studies to develop PTV and EZE immediate-release combination tablets on a large production scale.

DECLARATIONS

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Ethical approval

None required.

Use of Artificial intelligence/Large language models

We also declare that we did not use Generative artificial intelligence (AI) and AI-assisted technologies in writing the manuscript.

Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Conflict of interest

No conflict of interest is associated with this work.

Contribution of authors

We declare that this work was done by the author(s) named in this article, and all liabilities pertaining to claims relating to the content of this article will be borne by the authors. Ji Eun Kim performed the experiments. Kang Min Kim and Jae Sung Pyo reviewed the manuscript and commented on the study design. Kang Min Kim and Ji Eun Kim drafted the manuscript and supervised the study.

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