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Original Article

Optimization of Linagliptin and Valsartan Bilayer Tablets Using Quality by Design

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ABSTRACT

Background and Objectives: The development of a bilayer tablet containing valsartan and linagliptin requires precise control of formulation and process variables to ensure consistent product quality. This study aimed to establish the design space of the bilayer tablet by applying a Quality by Design (QbD) approach, thereby optimizing key formulation and process parameters to meet predefined Critical Quality Attributes (CQAs). **Materials and Methods:** A 2^3+3 full-factorial Design of Experiments (DoE) was implemented to investigate the effects of formulation factors, including microcrystalline cellulose and crospovidone and the process parameter, main compression force. CQAs, including hardness, friability, disintegration time, assay, content uniformity, and dissolution rate, were evaluated using Design Expert software. Statistical analysis was performed through Analysis of Variance (ANOVA) to identify significant factors influencing each CQA. **Results:** ANOVA results indicated that the main compression force significantly affected tablet hardness, friability, disintegration time, and dissolution rate (p<0.05). Additionally, microcrystalline cellulose and crospovidone showed a significant impact on disintegration time of valsartan (p<0.05). The optimized formulation and process ranges that satisfied all CQAs were determined as follows: microcrystalline cellulose (7-40%), crospovidone (4-13%), and main compression force (1070-1570 kgf). **Conclusion:** Through the QbD-based DoE study, the optimal design space for the bilayer tablet of linagliptin and valsartan was successfully established. The findings demonstrate that systematic formulation and process optimization can effectively ensure the desired product quality and performance.

Keywords: Bilayer Tablet, Design of Experiment, Linagliptin, Quality by Design, Valsartan.

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INTRODUCTION

Bilayer tablets enable the combination of two drugs within a single formulation. This design can separate incompatible compounds into distinct layers and enhance patient convenience and adherence.[1] It ensures precise dosing, thereby maximizing therapeutic effects and minimizing the risk of dosing errors.[2]

Linagliptin is an antidiabetic agent indicated for the treatment of patients with Type 2 Diabetes Mellitus (T2DM). By inhibiting Dipeptidyl Peptidase-4 (DPP-4), the enzyme that degrades incretin hormones, it enhances insulin secretion and reduces blood glucose levels.[3,4] Unlike other DPP-4 inhibitors, linagliptin is primarily excreted via a non-renal route through fecal elimination. This pharmacokinetic property renders it a suitable option for patients with impaired renal function.[5,6] Patients with T2DM frequently present with concomitant hypertension, which further exacerbates the risk of developing atherosclerotic cardiovascular diseases. Therefore, comprehensive management addressing both T2DM and hypertension is essential to mitigate the risk of serious vascular complications.[7]

Valsartan is an angiotensin II receptor antagonist blocker that is widely employed in the management of hypertension. It exhibits a dose-dependent efficacy in reducing both Systolic Blood Pressure (SBP) and Diastolic Blood Pressure (DBP) within a once-daily dosage range of 80-320 mg.[8] By selectively inhibiting the binding of angiotensin II to the AT1 receptor, it facilitates vasodilation and enhances systemic blood flow, thereby

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contributing to the reduction of blood pressure.[9,10] In addition to its antihypertensive effects, valsartan has demonstrated the ability to reduce albuminuria in patients with T2DM, offering potential therapeutic benefits for individuals with both hypertension and T2DM complications.[11]

QbD is a systematic approach to pharmaceutical development that focuses on product and process understanding, supported by scientific knowledge and quality risk management.[12] The International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) guidelines—ICH Q8 (Pharmaceutical Development), ICH Q9 (Quality Risk Management), and ICH Q10 (Pharmaceutical Quality System)—highlight the importance of QbD in ensuring consistent drug quality.[13] To implement QbD, a Quality Target Product Profile (QTPP) is first defined based on prior knowledge, and the CQA that affect the QTPP are identified.[14] Key factors such as Critical Material Attributes (CMA) and Critical Process Parameters (CPP) are then selected.[15] Using statistical tools, the influence of these variables on product quality is assessed, and a Design space (DS) is established to define the acceptable range for robust and consistent manufacturing.[16]

In this study, a QbD approach was applied to optimize a bilayer tablet formulation of linagliptin and valsartan. Factors identified as CMA and CPP were evaluated using a 2^3 + 3 full factorial design within the DoE. Based on the analysis of response variables, a DS was successfully established.

MATERIALS AND METHODS

Samples and Reagents

Linagliptin was purchased from Glenmark Pharmaceuticals (India). Valsartan was purchased from Zhejiang Tianyu Pharmaceutical Co. (China), Ltd. Colloidal silicon dioxide, crospovidone, low-substituted hydroxypropyl cellulose (L-HPC), pregelatinized starch and yellow ferric oxide were purchased from Whawon and Masung Co, Ltd (Korea). D-Mannitol was obtained from Roquette (France), Kollidon VA 64 was obtained from BASF Pharma (Germany). Dicalcium phosphate, magnesium stearate and microcrystalline cellulose were provided by Daewoo pharmaceutical Co. Ltd., (Korea). All other reagents were purchased from Sigma-Aldrich (USA). In the comparative dissolution study, Trajenta® 5 mg, manufactured by Boehringer Ingelheim (Germany) was used as the reference product for linagliptin and Diovan® 80 mg, manufactured by Novartis (Switzerland), was used as the reference product for valsartan.

Preparation of the Immediate-release Layer containing Linagliptin

The immediate-release layer containing linagliptin was prepared using a wet granulation method with water as the granulating fluid. First, linagliptin (5 mg/tablet), the Active Pharmaceutical Ingredient (API), was blended with dicalcium phosphate to enhance the stability of the drug substance. Subsequently, D-mannitol, pregelatinized starch, Kollidon® VA 64, and yellow ferric oxide were added and mixed thoroughly. The resulting mixture was granulated by the addition of water. The wet granules were dried at 70℃ until the Loss on Drying (LOD) reached 1.5-2.0%, as determined using a halogen moisture analyzer (MB90; OHAUS, USA). The dried granules were then passed through a 600 μm mesh sieve. Finally, magnesium stearate was added to the granules to improve lubrication, and the mixture was blended to complete the preparation.

Preparation of the Immediate-release Layer containing Valsartan

The immediate-release layer containing valsartan was prepared using a wet granulation method with water as the granulating fluid. First, valsartan (80 mg/tablet), the API, was sieved through an 850 μm mesh to achieve a uniform particle size. The sieved valsartan was blended with microcrystalline cellulose, L-HPC, and crospovidone. The blend was then granulated by gradually adding water. The wet granules were dried at 70℃ until the LOD reached 1.5-2.0%, as determined using a halogen moisture analyzer. After drying, the granules were passed through a 600 μm mesh to achieve a consistent granule size. Finally, colloidal silicon dioxide and magnesium stearate were added to the dried granules to improve flowability and lubrication, and the mixture was blended thoroughly.

Manufacture of a Bilayer Tablet containing Linagliptin and Valsartan

A bilayer tablet with a total weight of 270 mg was manufactured using a multi-layer tablet press (Autotab-200TR; Ichihashi Seiki Co., Ltd. Japan), containing valsartan granules (150 mg) and linagliptin granules (120 mg).

Risk Assessment

The risks associated with each factor in the formulation and manufacturing process were evaluated for their potential impact on CQA through an initial risk assessment. Failure Mode and Effects Analysis (FMEA) was utilized as a quality risk management tool to identify factors that may influence CQA. Based on prior research and accumulated knowledge, the risks were classified as low, medium, or high. Factors identified as having a high impact were prioritized for further analysis.[17]

Design of Experiment using 2^3 + 3 Full Factorial Design

In the development of the Valsartan immediate-release layer formulation, an initial risk assessment was conducted based on prior research to evaluate the impact of CMA and CPP on the CQA of the bilayer tablet formulation.

To determine the optimal range for formulation development, experimental points were designed using a 2^3 + 3 full factorial design with Design Expert software version 13 (Stat-Ease Inc.). In the design, the factors included CMA, such as microcrystalline cellulose (A) and crospovidone (B), and CPP, including the main compression force (C). The levels for microcrystalline cellulose were set at 5, 10 and 15%, for crospovidone at 2, 5 and 8%, and for the main compression force at 1200, 1500 and 1800 kgf. The responses corresponding to these factors were evaluated for CQA, including hardness (Y_1), friability (Y_2), disintegration time (Y_3, Y_4), assay (Y_5, Y_6), content uniformity (Y_7, Y_8), and dissolution rate (Y_9, Y_{10}). The targets and acceptable ranges for each response are summarized in Table 1.

Hardness

Hardness was measured using a hardness tester (TBH 325; Erweka GmbH, Germany). Three tablets per batch were randomly selected and measured.

Friability test

Friability was evaluated using a friability tester (FR-2000; Copley Scientific Limited, Nottingham, UK). The initial weight (W_1) of ten tablets was recorded, followed by rotation at 25 rpm for 4 min. The final weight (W_2) was then measured, and friability was determined using the following formula:

$$\text{Friability (\%)} = \frac{(W_1 - W_2)}{W_1} \times 100$$

Disintegration Time

Disintegration time was measured using a disintegration tester (KDIT 200, Kukje Engineering Co.). The time required for complete disintegration of the bilayer tablet in water at 37 ± 2°C was determined.

Estimation of Drug Content

The drug contents of linagliptin and valsartan were analyzed by HPLC. Linagliptin and valsartan were detected at wavelengths of 295 nm and 242 nm, respectively. The mobile phase consisted of 37% acetonitrile containing 0.5% formic acid. The chromatographic conditions were as follows: (a) column: Vision HT C18 HL (150 mm × 4.6 mm, 5 µm particle size), (b) flow rate: 1.2 mL/min, (c) column oven temperature: 40°C, (d) total run time: 10 min, and (e) injection volume: 5 µL.

For sample preparation, the tablet was placed in a flask, and the volume was adjusted to 50 mL using a mixture of water and acetonitrile (1:1, v/v). The solution was stirred for approximately 1 hr and then filtered through a 0.45 µm RC filter prior to determination.

The same procedure was applied to 10 tablets to evaluate the content uniformity, and the formulation was considered to comply if the Acceptance Value (AV) was not more than 15.

In vitro Dissolution Test

The dissolution test was performed using USP apparatus 2 (paddle method, 50 rpm) in 900 mL of pH 4.5 buffer at 37 ± 0.5°C. Samples (2 mL) were withdrawn at 10, 15, 30, 45, and 60 min and filtered through a 0.45 µm RC filter prior to determination. The samples were analyzed using the HPLC conditions previously described.

According to KFDA guidelines for pharmaceutical equivalence, dissolution profile similarity between the test and reference tablets was evaluated using the similarity factor (f2). The formula is as follows:

$$f2 = 50 \times \log\left\{\left[1 + \left(\frac{1}{n}\right)\sum_{t=1}^{n}(R_t - T_t)^2\right]^{-0.5} \times 100\right\}$$

where n, is the number of time points, R_t, the average dissolution rate of the reference tablet, and T_t, the average dissolution rate of the test tablet. A f2 value of 50 or above at pH 4.5 was considered to indicate equivalence.

Statistical Analysis

The data were analyzed using Design Expert software version 13 (Stat-Ease Inc.; USA). ANOVA was performed, and statistical parameters, including the p-value, F-value, and coefficient of determination (R^2), were calculated.

RESULTS

Initial risk assessment of bi-layer tablet containing linagliptin and valsartan

Based on prior knowledge and preliminary assessments, microcrystalline cellulose and crospovidone were identified as excipients associated with a "high" level of risk in the immediate-release layer of valsartan. Likewise, the main compression force applied during tablet compression was evaluated as a high-risk process parameter. These risk assessments are summarized in Table 2.

Microcrystalline cellulose, due to its porous structure and water-absorbing properties, has the potential to influence the release behavior of the active pharmaceutical ingredient.[18] Crospovidone, commonly employed as a disintegrant, exhibits concentration-dependent effects on drug release kinetics.[19] Furthermore, the main compression force significantly affects multiple critical quality attributes including tablet hardness, friability, disintegration time, and dissolution rate, thereby supporting its classification as a high-risk level.[20]

DoE study for Formulation Optimization

DoE was applied to evaluate the optimal conditions for microcrystalline cellulose and crospovidone, selected as CMA, and main compression force, identified as a CPP. A 2^3+3 full factorial design was employed, and the effects of each independent variable (microcrystalline cellulose, crospovidone, main compression force) on the dependent variables (assay, content

uniformity, hardness, friability, disintegration, dissolution rate) are summarized in Table 3.

As a result, tablet hardness was found to range from 6.1 to 9.9 kp, and friability was measured between 0.31% and 0.44%. The disintegration time of linagliptin ranged from 3 to 7.4 min, with some batches falling outside the acceptance criteria (4-8 min), while valsartan disintegrated within 0.5 to 3.8 min. In the assay test, the content of linagliptin ranged from 98.27% to 101.41%, and that of valsartan ranged from 97.86% to 99.8%. For content uniformity, the AV of linagliptin ranged from 0.93% to 2.4%, and that of valsartan from 1.28% to 3.13%, all of which were within the specified limits. In the dissolution test under pH 4.5 conditions, the dissolution rate of linagliptin at 15 min ranged from 67.13% to 96.86%, with some batches falling below the acceptance criterion (≥ 85%). The f2 values for valsartan were between 50.97 and 68.62.

ANOVA, DS, and Updated Risk Assessment

Based on the results presented in Table 3, statistical parameters such as the coefficient of determination (R^2), *p*-values indicating model significance, and lack-of-fit tests evaluating model adequacy were derived and are summarized in Table 4.[21] A *p*-value less than 0.05 was considered to indicate statistical significance.

Except for models in which no main effects were identified, all showed statistically significant *p*-values (<0.05), with lack-of-fit tests indicating no significance ($p \geq 0.05$).

Further analysis of the ANOVA results in Table 4 revealed the specific influence of each factor (A: microcrystalline cellulose, B: crospovidone, C: main compression force) on the respective CQA. No significant factors were identified for the assay and content uniformity of both APIs. The hardness of the bilayer tablets was significantly influenced by factor C ($p=0.0420$), while friability was affected by the interaction between factors A and C ($p=0.0255$). The disintegration time of linagliptin was significantly affected by factor C ($p=0.0004$), whereas the disintegration time of valsartan was influenced by factors A ($p=0.0183$), B ($p=0.0090$), and C ($p=0.0003$). In terms of dissolution, linagliptin was influenced by factor C ($p=0.0031$) and the interactions AB ($p=0.0016$), AC ($p=0.0130$), and ABC ($p=0.0022$), while valsartan was affected by factors B ($p=0.0240$), C ($p=0.0021$), and the interactions BC ($p=0.0064$) and ABC ($p=0.0368$).

Figure 1 illustrates the contour plots depicting the effects of the main factors on each CQA. The ranges of factor levels that meet the optimization criteria were identified in this study, and the DS is shown in Figure 2. The white dot represents the center point, which was replicated three times, and the black area surrounding this point indicates the region where all quality attributes are satisfied.

The ranges of CMA and CPP that satisfied all CQAs were identified as follows: microcrystalline cellulose (7-40%), crospovidone (4-13%), and main compression force (1070-1570 kgf). These results demonstrate that both excipient levels and process parameters have relatively broad design spaces, allowing for a robust and flexible formulation.

Through the systematic optimization of factors affecting hardness, friability, disintegration time, dissolution, assay, and

Table 1: Factors and responses of 2^3 + 3 full factorial design for DoE.

Factor			Level		
			-1	0	+1
CMA	A	Microcrystalline cellulose (%)	5	10	15
	B	Crospovidone (%)	2	5	8
CPP	C	Main compression (kgf)	1200	1500	1800

Response		Goal	Acceptable ranges
Y_1	Hardness (kp)	In range	$6.0 \leq Y_1 \leq 10.0$
Y_2	Friability (%)	Minimize	$Y_2 \leq 0.5$
Y_3	Disintegration of Linagliptin (min)	In range	$4.0 \leq Y_3 \leq 8.0$
Y_4	Disintegration of Valsartan (min)	In range	$0.5 \leq Y_4 \leq 4.5$
Y_5	Assay of Linagliptin (%)	In range	$95.0 \leq Y_5 \leq 105.0$
Y_6	Assay of Valsartan (%)	In range	$95.0 \leq Y_6 \leq 105.0$
Y_7	Content uniformity of Linagliptin (%)	Minimize	$Y_7 \leq 15$
Y_8	Content uniformity of Valsartan (%)	Minimize	$Y_8 \leq 15$
Y_9	Dissolution rate of Linagliptin at 15 min in pH 4.5 (%)	Maximize	$Y_9 \geq 85$
Y_{10}	f2 value of Valsartan in pH 4.5 (f2 value at 10, 15, 30, 45, 60 min)	Maximize	$Y_{10} \geq 50$

Table 2: Initial risk assessment of bilayer tablet containing linagliptin and valsartan.

Material and process variables	Drug Product CQA					
	Hardness	Friability	Disintegration	Assay	Content uniformity	Dissolution
Microcrystalline cellulose	Low	Low	High	Low	Low	High
Low-substituted hydroxypropyl cellulose	Low	Low	Low	Low	Low	High
Crospovidone	Low	Low	High	Low	Low	High
Colloidal silicon dioxide	Low	Low	Low	Low	Low	Low
Magnesium stearate	Low	Low	Low	Low	Low	Low
Pre-compression force	Low	Low	Low	Low	Low	Low
Main compression force	High	High	High	Medium	Medium	High

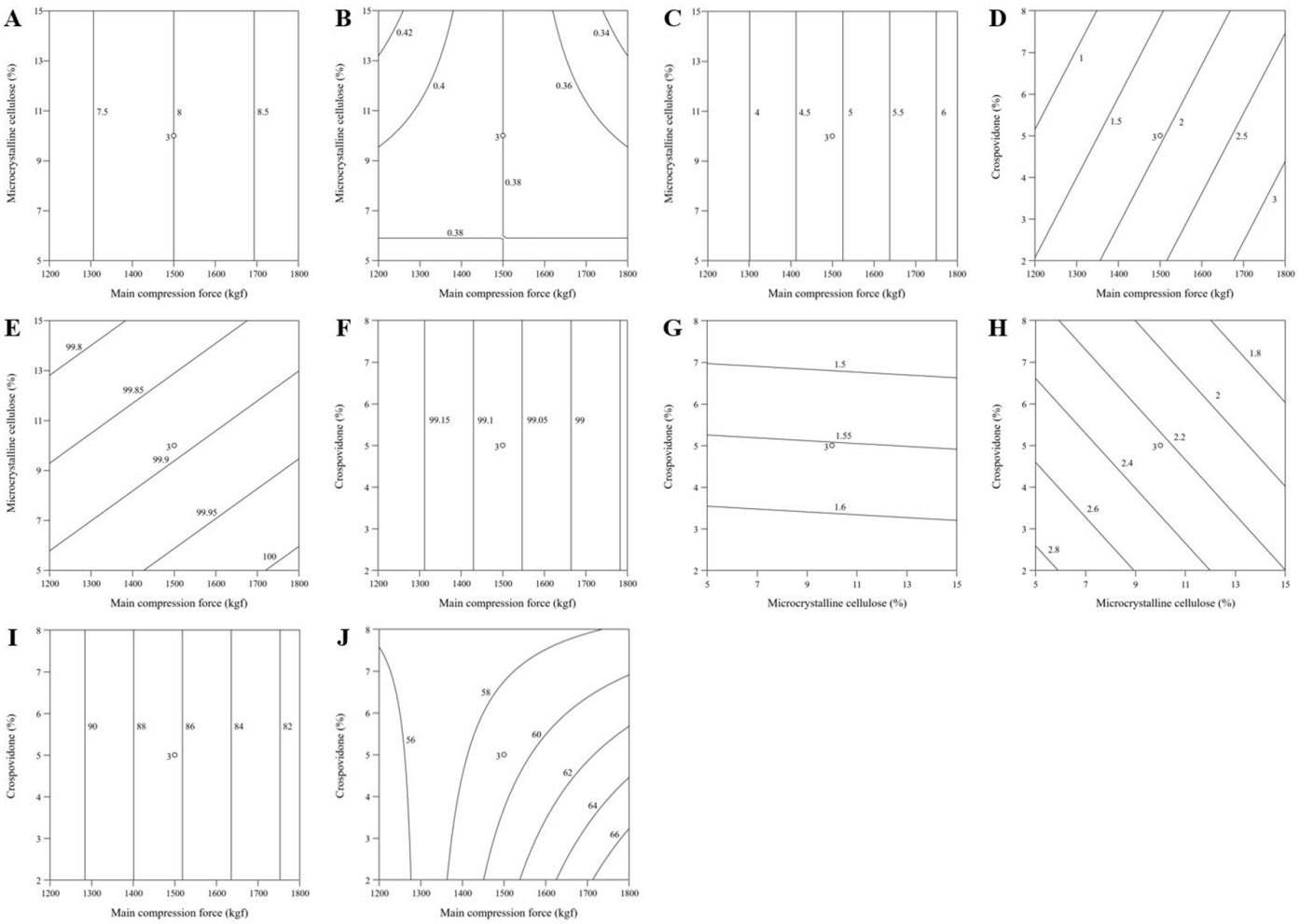

Figure 1: Main effect of microcrystalline cellulose, crospovidone and main compression force on (A) Hardness, (B) Friability, (C) Disintegration of linagliptin, (D) Disintegration of valsartan, (E) Assay of linagliptin, (F) Assay of valsartan, (G) Content uniformity of linagliptin, (H) Content uniformity of valsartan, (I) Dissolution rate of linagliptin at 15 min in pH 4.5, (J) f2 value of valsartan in pH 4.5. ○; center points (n=3).

Table 3: Factor values and results of the response for each batch of a 2^3 + 3 full factorial design.

BatchNo.	Factors: Material Attribute		Factor: Process Parameter	Responses									
	A	B	C	Y_1	Y_2	Y_3	Y_4	Y_5	Y_6	Y_7	Y_8	Y_9	Y_{10}
	(%)	(%)	(kgf)	(kp)	(%)	(min)	(min)	(%)	(%)	(AV)	(AV)	(%)	(f2)
1	15	8	1200	6.70	0.44	4.02	0.72	99.02	99.27	1.52	1.69	87.25	54.68
2	15	2	1200	7.62	0.42	4.01	1.82	98.27	99.11	2.04	2.26	86.09	57.53
3	5	8	1800	9.18	0.42	5.69	1.46	98.88	98.75	1.92	3.13	67.13	56.68
4	10	5	1500	9.13	0.36	4.71	1.18	99.11	99.80	1.65	2.56	87.65	57.05
5	5	2	1200	8.51	0.39	3.23	1.12	99.78	99.17	0.98	2.71	96.86	50.97
6	5	2	1800	9.90	0.35	5.77	3.14	100.38	98.54	2.40	2.77	92.44	68.62
7	10	5	1500	8.20	0.31	5.06	1.66	99.17	97.86	1.88	2.87	83.96	60.55
8	15	2	1800	7.76	0.31	7.44	3.78	99.73	99.63	1.14	2.38	71.07	67.40
9	10	5	1500	8.22	0.32	5.32	1.69	99.19	99.28	0.95	2.41	84.76	59.25
10	5	8	1200	6.11	0.36	3.01	0.53	101.41	99.24	0.93	1.63	95.56	57.58
11	15	8	1800	8.17	0.35	6.03	3.20	100.18	98.85	1.49	1.28	94.12	59.77

content uniformity, the risks associated with excipient selection and process parameters were effectively reduced. Accordingly, the bilayer tablet formulation of linagliptin and valsartan was successfully optimized to achieve the desired quality attributes.

DISCUSSION

This study aimed to optimize the bilayer tablet formulation of linagliptin and valsartan using a DoE approach. DoE is a systematic and statistically sound method that uses mathematical models to explore the relationships between input factors and output responses, helping to establish control strategies for pharmaceutical quality. A 2^3+3 full factorial design was employed to investigate the effects of formulation and process factors, with the experimental results summarized in Table 3. The ANOVA results, presented in Table 4, identified the key factors influencing each CQA. Based on these findings, Figure 1 illustrates the effects of formulation factors on the CQA. Figure 2 shows the DS, which defines the optimal ranges of formulation parameters that ensure all CQA are satisfied. In Figure 2, the black area shows the robust design space where all CQA are within target specifications, and the white dot indicates the center point of the design.

Hardness was primarily influenced by the main compression force, with the results presented in Table 2 indicating that all batches were within the acceptable range. It is well established that tablet hardness generally increases with compression force, a trend that was also observed in Figure 1A, where higher compression force corresponded to increased hardness.[22] While excipients may affect hardness through the formation of hydrogen bonds between particles during compression, the ANOVA results identified only the main compression force as having a significant impact on hardness, suggesting that excipients did not have a significant effect in this study.[23]

As shown in Table 4, friability was not significantly affected by any single factor but was influenced by the interaction between microcrystalline cellulose and the main compression force. According to Shipar *et al.* (2014), friability tends to decrease as tablet hardness increases.[24] However, in this study, friability was not affected by the main compression force, which was identified as the primary factor influencing hardness.

For the disintegration test, the *p*-values for the effect of the main compression force on the disintegration of linagliptin and valsartan were 0.0004 and 0.0003, respectively, suggesting that the main compression force was an important factor commonly affecting the disintegration of both layers in the bilayer tablet. It is generally known that higher compression forces tend to slow down tablet disintegration.[25] In line with this, Figure 1C and 1D in this study also showed that the disintegration time became longer as the compression force increased. These results confirm that the main compression force was confirmed to have a significant impact in determining the disintegration of both layers. In addition, microcrystalline cellulose (p=0.0183) and crospovidone (p=0.0090) were identified as significant factors specifically affecting the disintegration of the valsartan layer. According to Yassin *et al.* (2015), microcrystalline cellulose has a porous structure and readily absorbs water, which likely contributed to its effect on valsartan disintegration.[18] Crospovidone is commonly used as a disintegrant in tablet formulations at a concentration of approximately 2-5%, controlling tablet disintegration.[26] Therefore, it is presumed that crospovidone also contributed to the disintegration of valsartan in this study.

In terms of drug content, the assay and content uniformity results for both linagliptin and valsartan were within the acceptable range, as shown in Table . Furthermore, the analysis of the experimental factors confirmed that none of the variables evaluated in this study had a significant impact on the assay or content uniformity of either drug, as presented in Table 4.

As presented in Table 4, the main compression force was identified as the primary factor significantly influencing the dissolution rate of linagliptin at 15 min in pH 4.5 buffer (p = 0.0031). This trend is further supported by Figure 1I, which shows a decrease in dissolution rate with an increasing compression force. The reference product used for comparison demonstrated a dissolution rate exceeding 85% at 15 min. In this study, the reduced dissolution rate of linagliptin under higher compression forces is considered to be associated with the prolonged disintegration time observed at these conditions.[25] Moreover, the dissolution rate of linagliptin at 15 min in pH 4.5 buffer was also affected by the interaction between microcrystalline cellulose and crospovidone (p=0.0016), that between microcrystalline cellulose and the main compression force (p=0.0130), as well as the three-way interaction among these factors (p=0.0022).

In the dissolution test of valsartan at pH 4.5, crospovidone (p=0.0240), main compression force (p=0.0021), the interaction between these two factors (p=0.0064), and the three-way interaction involving microcrystalline cellulose (p=0.0368) were identified as significant influencing factors (Table). As shown by the f2 values of valsartan for each batch at pH 4.5 in Table , higher f2 values were observed when the proportion of crospovidone was low and the main compression force was high. Generally, crospovidone accelerates disintegration, while higher compression forces tend to delay it.[25,26] Therefore, in batches with a lower proportion of disintegrant and higher compression force, the disintegration time of valsartan was prolonged, which likely contributed to greater similarity with the reference product. This trend is also evident in Figure 1J, where higher f2 values were consistently observed as the crospovidone content decreased and the main compression force increased.

Figure 2 illustrates the DS for the CQA of the linagliptin and valsartan bilayer tablet, including hardness, friability, disintegration, assay, content uniformity, and dissolution. Although microcrystalline cellulose was identified as a factor influencing the disintegration of valsartan, its levels in all batches remained within acceptable limits, and the other two factors were found to have more significant impacts on multiple CQAs. Therefore, the DS was primarily defined in terms of crospovidone and the main compression force. Based on the analysis, the ranges

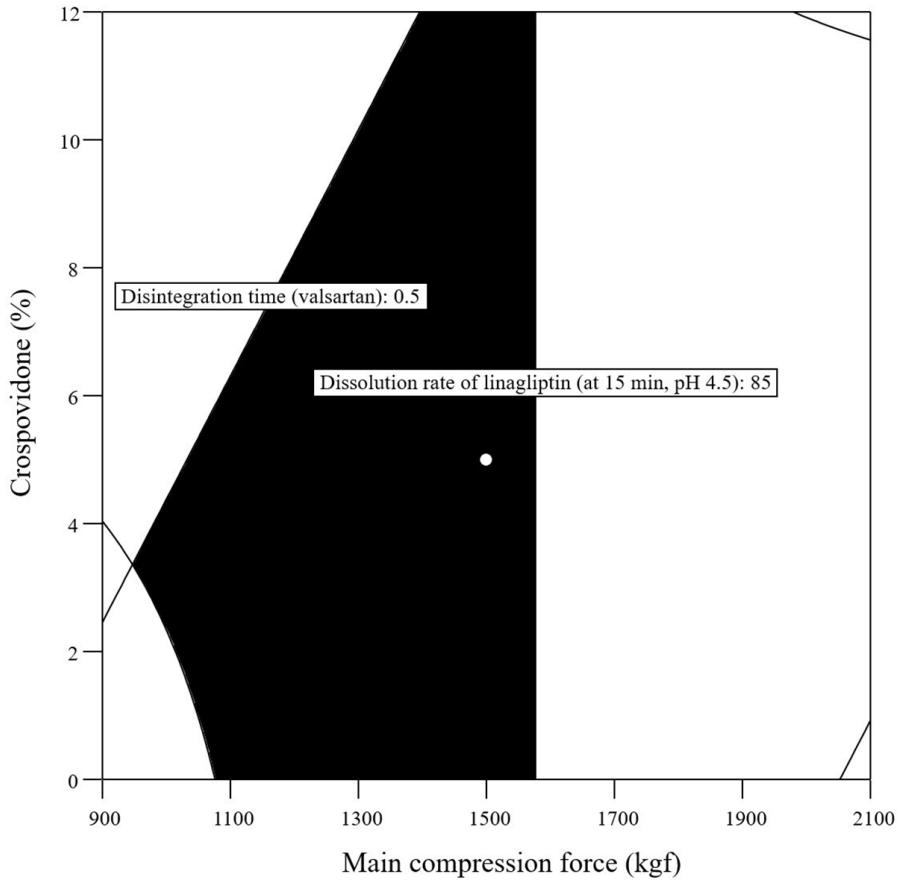

Figure 2: Design space of the bilayer tablet containing linagliptin and valsartan depending on crospovidone and main compression force. ○; center points (n=3).

Table 4: ANOVA results of the 2^3+3 full factorial design.

Resoponse	Source	Sum of squares	d_f[a]	Mean square	F-value	*p*-value	R^2
Hardness	Model	4.80	1	4.80	5.85	0.0420	0.4222
	C	4.80	1	4.80	5.85	0.0420	
	Lack of fit	6.04	6	1.01	3.73	0.2267	
Friability	Model	0.0101	2	0.0051	6.67	0.0239	0.6558
	C	0.0040	1	0.0040	5.35	0.0540	
	AC	0.0061	1	0.0061	7.99	0.0255	
	Lack of fit	0.0039	5	0.0008	1.11	0.5355	
Disintegration of linagliptin	Model	14.67	2	7.34	20.19	0.0012	0.8523
	C	14.31	1	14.31	39.40	0.0004	
	Lack of fit	2.36	5	0.4713	5.05	0.1735	
Disintegration of valsartan	Model	10.29	3	3.43	26.01	0.0008	0.9286
	A	1.36	1	1.36	10.32	0.0183	
	B	1.90	1	1.90	14.41	0.0090	
	C	7.03	1	7.03	53.29	0.0003	
	Lack of fit	0.6250	4	0.1562	1.87	0.3767	
Assay of linagliptin	Model	0.1320	4	0.0330	1.88	0.2522	0.6006
	Lack of fit	0.0229	3	0.0076	0.2360	0.8663	
Assay of valsartan	Model	0.6301	4	0.1575	0.3560	0.8306	0.2217
	Lack of fit	0.1957	3	0.0652	0.0647	0.9737	
Content uniformity of linagliptin	Model	1.94	1	0.3882	3.05	0.1515	0.7920
	Lack of fit	0.0404	2	0.0202	0.0861	0.9207	
Content uniformity of valsartan	Model	2.27	4	0.5663	3.75	0.0897	0.7502
	Lack of fit	0.6441	3	0.2147	3.90	0.2107	
Dissolution rate of linagliptin at 15 min in pH 4.5	Model	895.94	6	149.32	55.32	0.0037	0.9910
	C	210.13	1	210.13	77.84	0.0031	
	AB	322.83	1	322.83	119.60	0.0016	
	AC	76.26	1	76.26	28.25	0.0130	
	ABC	263.35	1	263.35	97.56	0.0022	
	Lack of fit	0.5618	1	0.5618	0.1491	0.7366	
f2 value of valsartan in pH 4.5	Model	252.50	5	50.50	20.25	0.0061	0.9620
	B	31.24	1	31.24	12.53	0.0240	
	C	125.69	1	125.69	50.40	0.0021	
	BC	68.04	1	68.04	27.28	0.0064	
	ABC	23.70	1	23.70	9.50	0.0368	
	Lack of fit	3.72	2	1.86	0.5936	0.6275	

that satisfy all CQAs are as follows: (A) microcrystalline cellulose: 7-40%, (B) crospovidone: 4-13%, and (C) main compression force: 1070-1570 kgf.

CONCLUSION

The development of a bilayer tablet containing linagliptin and valsartan, utilizing a DoE approach for the management of hypertension and T2DM complications, successfully identified the factors that significantly influence product quality. In the wet granulation process, the proportion of microcrystalline cellulose was found to have a significant effect on the disintegration of the valsartan layer, while the proportion of crospovidone significantly affected both the disintegration and dissolution of valsartan. The main compression force was identified as a critical factor influencing tablet hardness, friability, disintegration, and dissolution. Through the determination of the optimal ranges for each factor, the bilayer tablet formulation containing linagliptin and valsartan was successfully optimized. Consequently, the development of this bilayer tablet is expected to improve patient compliance and support effective treatment outcomes for patients with these comorbid conditions.

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ABBREVIATIONS

ANOVA: The Analysis of variance; **API:** Active pharmaceutical ingredient; **AV:** Acceptance value; **CMAs:** Critical material attributes; **CPP:** Critical process parameters; **CQAs:** The Critical quality attributes; **DBP:** Diastolic blood pressure; **DoE:** Design of experiments; **DPP-4:** Dipeptidyl peptidase-4; **DS:** Design space; **FMEA:** Failure mode and effects analysis; **HPLC:** High-Performance Liquid Chromatography; **ICH:** International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use; **kP:** Kilopond; **LOD:** Loss on drying; **T2DM:** Type 2 diabetes mellitus; **L-HPC:** Low-substituted hydroxypropyl cellulose; **QTPP:** Quality target product profile; **QbD:** Quality by design; **SBP:** Systolic blood pressure.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

SUMMARY

Linagliptin and valsartan bilayer tablet was investigated the ranges of tablet compression and excipients for drug product through design of experiments. Microcrystalline cellulose: 23%, crospovidone: 8.5%, and main-compression forces: 1320 kgf were optimal ranges for drug product.

The identification of the ranges for tablet compression will produce high quality products.

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