Ind. J. Pharm. Edu. Res., 2024; 58(3):730-735.
https://www.ijper.org

Original Article

Tablet Compression Optimization of Ivabradine Sustained-Release Tablet Using Full Factorial Design

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ABSTRACT

Aim: This study aimed to qualitatively identify the ranges of the factors involved in the tablet compression process for ivabradine Sustained Release (SR) tablets. **Materials and Methods:** A full factorial design of experiments study was used to identify three factors (pre- and main-compression force and paddle rotation time) involved in the compression process of ivabradine SR tablets. For robust tableting, three responses (content uniformity, friability, and dissolution) were evaluated as critical quality attributes via analysis of variance using Design Expert software. **Results:** The main compression force significantly influenced dissolution (1 hr, $p<0.0001$; 3 hr, $p<0.0001$; and 8 hr, $p=0.0002$). Precompression and paddle rotation time slightly influenced friability ($p=0.0510$) and content uniformity ($p=0.0968$). These results showed that paddle rotation time (0.27-1.37 sec), pre-compression (1.5 kN), and main compression (7.7-9.2 kN) influenced the tablet compression process of the optimal ivabradine SR tablet. **Conclusion:** In summary, robust ranges of three factors for tableting were successfully evaluated. It can be concluded that the ranges of tablet compression leading to high quality (low friability and content uniformity, and optimal dissolution) for tableting were successfully observed by the DoE approach.

Keywords: Design of experiment, Ivabradine, Quality by design, Sustained-release tablet.

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Received: 23-02-2023;
Revised: 19-01-2024;
Accepted: 19-01-2024.

INTRODUCTION

Chronic angina is defined as chest pain or discomfort caused by exercise or emotional stress caused by an imbalance between myocardial oxygen supply and consumption.[1,2] The American College of Cardiology and American Heart Association (ACC/AHA) guidelines recommend single or complex prescriptions, such as calcium channel blockers, short- and long-acting nitrates, beta-blockers, and potassium channel activators, for chronic angina.[3] Ivabradine hydrochloride (Procoralan®) reduces heart rate by selectively inhibiting the I_f channel of the sinoatrial node, which is activated by hyperpolarization and regulated by the autonomic nervous system.[4,5] According to the recommendations of the European Medicines Agency (EMA), ivabradine is approved for the treatment of chronic stable angina with a heart rate of over 70 beats per minute in adults who cannot use beta-blockers with normal sinus rhythm.[4,6]

In drug delivery systems, oral administration is the preferred option for various administration forms, such as immediate release, controlled release, and Sustained Release (SR). SR is widely used in drug development to reduce side effects by reducing drug administration frequency and preventing changes in the concentration.[7,8] Currently, ivabradine is developed as an immediate-release tablet, and it is necessary to develop an SR tablet for patient convenience and compliance. Drug development should be developed to meet patient needs and achieve the target quality. Quality control of the drugs is necessary to ensure their efficacy and safety.[9] Quality by Design (QbD) is a scientific, systematic, risk-based approach to each process parameter based on knowledge of drug development.[10] In drug development, there is always uncertainty in the process; therefore, risk management is important for eliminating this uncertainty.[9] The International Conference on Harmonization (ICH) Q8 guidelines represent process design based on quality control and scientific application.[11]

This study aimed to develop an optical tablet compression process for ivabradine SR tablets using DoE. A three-level full factorial design with three factors (pre- and main-compression force and paddle rotation time) was used for optimization. The independent variables of the three factors in the process were

DOI: 10.5530/ijper.58.3.81

evaluated by measuring content uniformity, dissolution (1, 3, and 8 hr), and friability.

MATERIALS AND METHODS

Samples and reagents

Ivabradine hydrochloride was obtained from Alembic Pharmaceuticals Co. Ltd., (Vadodara, India). Microcrystalline Cellulose (MCC 101), dicalcium phosphate, hydroxypropyl methylcellulose (K200M), colloidal silicon dioxide (Aerosil®), and magnesium stearate were purchased from Masung Ltd., (Seoul, Korea). Acetonitrile was of High-Performance Liquid Chromatography (HPLC) grade and obtained from Duksan reagents (Ansan, Korea).

Manufacture of the ivabradine SR tablets

The ivabradine SR formulation (180 mg per tablet) was manufactured using a wet granulation (Nara Machinery Co. Ltd., NMG-1L, Tokyo, Japan) method. Ivabradine (10.78 mg) was mixed with microcrystalline cellulose (101.82 mg) and hydroxypropyl methylcellulose (50 mg). Distilled water (130 mg) was added for wet granulation of the mixture. The granules were dried at 7°C for 2 hr in a dry oven (OF-22GW, Jeio Tech, Daejeon, Korea), with a Loss on Drying (LoD) of approximately 2.2% (w/w), and sieved using a Comil sieve (K-50, Eur-Asia, Seoul, Korea) with a 600 μm screen at 600 rpm. After the screening, dicalcium phosphate (14.7 mg), colloidal silicon dioxide (0.9 mg), and magnesium stearate (1.8 mg) were blended into the granules. The tablets were compressed using a single tablet press (Autotab-200TR, Japan).

Risk assessments and DoE study

For the initial risk assessment of the tablet compression process before the DoE study, three responses (content uniformity, friability, and dissolution, such as critical quality attributes (CQAs)) were determined as risks (high) of responses in the tableting process of the ivabradine SR tablet (Table 1). The selected risk assessment of the tableting (pre- and main-compression force, and paddle rotation time) process that may affect quality attributes, such as pre- and main-compression force and paddle rotation time, is shown in Table 2.[12] A three-factor (pre- and main-compression force and paddle rotation time), three-level, full factorial design was also used to optimize the process, as shown in Table 2. Eleven formulations (200 g per formulation) were prepared by the tableting press for the DoE study and analyzed using Design Expert software version 13.0.5.0 (Stat-Ease Inc., Minneapolis, MN, USA) (Table 3). We identified whether pre- and main- compression force and paddle rotation time for the tableting process had an impact on content uniformity, friability, and dissolution affecting the drug product (Table 3).

Loss on Drying (LOD)

Moisture content was measured using a halogen moisture analyzer (MB90, Ohaus, Seoul, Korea) exposed to 105°C for 15 min.

Hardness

A tablet hardness tester (8M, Dr. Schleuniger, Switzerland) was used to test for tablet hardness. Five tablets per batch were randomly selected and identified.

Friability test

A friability test for assessing the friability of the tablet (n=20) was performed using a friability tester (FR-2000, Nottingham, United Kingdom) at 25 rpm for 4 min.

Content uniformity

Content uniformity test was performed by the modified method of Lodhi *et al.*[13]

Dissolution testing

The dissolution tests of tablets at pH 6.8 (900 mL; time points: 1, 3, and 8 hr) were performed using the basket method (USP apparatus 1, 100 rpm).

High-Performance Liquid Chromatography (HPLC) Conditions

The dissolution values were analyzed by using the following method: (a) detection: 220 nm, (b) column: Discovery RP-Amide C16, 4.6 mm×150 mm, 5 μm, (c) column temperature: 40°C, (d) mobile phase: 85% orthophosphoric acid in 0.1 M KH_2PO_4 (pH=3): acetonitrile=80:20, € flow rate: 1.6 mL/min, (f) analysis time: 6 min.

Statistical analysis

All statistical analyses were evaluated with a full-factorial design using Design Expert software version 13.0.5.0 (Stat-Ease Inc., Minneapolis, MN, USA) for p-values<0.05, F test, coefficient of determination (R^2), and adjusted coefficient of determination (adjusted R^2) parameters.

RESULTS

Initial risk evaluation in the tableting process of ivabradine SR tablets

Table 1 shows the initial risk assessment of the tableting processes for ivabradine SR tablets. An initial risk assessment was conducted to determine which tableting process potentially affected CQAs. The initial risk assessment was evaluated based on the initial experimental data and prior formulation knowledge (Table 1).[12] Table 1 shows the process variables evaluated on a three-level scale (high, medium, and low). Paddle rotation time and pre- and main-compression force were individually identified as

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

Process variables		Drug Product CQA		
		Content uniformity	Dissolution	Friability
Pre-compression force		Low	Low	High
	Main compression force	Low	High	High
	Paddle rotation time	High	High	Low

Table 2: 2^3 full factorial design for DoE of tablet compression process.

Factors: Process Parameters			Range and Levels		
			-1	0	+1
X_1	Pre-compression force (kN)		1.0	1.5	2.0
X_2	Main compression force (kN)		5.4	7.4	9.4
X_3	Paddle rotation time (sec)		0.6	1	1.5
Responses		Goal	Acceptable ranges		
Y_1	Content uniformity (%)	Minimize	$Y_1<5.0$		
Y_2	Friability (%)	Minimize	$Y_2<0.5$		
Y_3	Dissolution at 1 hr (%)	In range	$20.0\leq Y_3\leq 40.0$		
Y_4	Dissolution at 3 hr (%)	In range	$40.0\leq Y_4\leq 60.0$		
Y_5	Dissolution at 8 hr (%)	In range	$Y_5\geq 80.0$		

"high risk" of content uniformity and dissolution, friability, and dissolution and friability.

Tablet-compression DoE study

Table 3 shows the DoE results for the factors (pre- and main compression force and paddle rotation time) and responses (content uniformity, friability, and dissolution) in the tableting process. These results show that the content uniformity (%) varied from 1.31 to 4.09, friability (%) from 0.20 to 0.40, dissolution (%; 1 hr) from 21.68 to 48.58, dissolution (%; 3 hr) from 42.43 to 69.86, and dissolution (%; 8 hr) from 67.77 to 95.53. According to the Analysis of Variance (ANOVA) results in Table 4, two factors (paddle rotation time and precompression force) nearly affected the responses of content uniformity (p=0.0968) and friability (p=0.0510) within the studied ranges. However, the main compression force of the independent factors strongly affected the dissolution (1 and 3 hr: $p<0.0001$; 8 hr: p=0.0002) of critical quality attributes. All models had values of $p<0.05$. The lack-of-fit had values of $p>0.05$. This means that these are the appropriate models for our adjustments (Table 4). Additionally, contour plots showed that all factors affected the response (Figure 1).

Design space, control strategy, and updated risk assessment

To identify the tablet compression process robustness, a design space (95% confidence interval) of the mean values of feeder paddle time and pre- and main-compression forces was drawn in Figure 2. The white parts indicate that the target goal values were not reached. The satisfied range for the targeted goal values was identified as black (Figure 1). The range of pre- and main-compression forces and paddle rotation time for the control strategy (CS) was well justified, with the following values: pre-compression force (approximately 1.5 kN), main compression force (approximately 7.2 kN), and paddle rotation time (approximately 1.0 s). The mean values of the three factors had the best range for all the responses. Acceptable ranges of parameters (pre- and main-compression forces and paddle rotation time) in the tableting satisfying all responses were pre-compression force (1.0-2.0 kN), main-compression force (6.5-10.0 kN), and paddle rotation time (0.2-1.77 s). In this study, the manufacturing process (tablet compression) with established ranges of factors impacting hardness, disintegration time, dissolution, and content uniformity were updated from high to low risks.

Table 3: Experimental results of the full factorial design DoE to study the tableting process variables.

	Factors: Process variables			Responses				
Batch No.	A: Pre-compression force	B: Main compression force	C: Paddle rotation time	Y_1: Content uniformity	Y_2: Friability	Y_3: Dissolution at 1 hr	Y_4: Dissolution at 3 hr	Y_5: Dissolution at 8 hr
	(kN)	(kN)	(sec)	(%)	(%)	(%)	(%)	(%)
1	2.0	5.4	0.5	4.09	0.27	41.52	65.42	94.76
2	1.0	5.4	1.5	1.37	0.22	46.65	69.58	93.94
3	1.5	7.4	1	2.14	0.26	29.93	50.04	80.01
4	1.0	9.4	1.5	1.97	0.34	24.18	46.85	78.45
5	2.0	9.4	0.5	3.88	0.21	22.05	42.43	62.56
6	1.5	7.4	1	2.16	0.24	29.93	49.96	79.94
7	2.0	5.4	1.5	1.31	0.21	44.16	69.86	94.81
8	1.0	9.4	0.5	4.07	0.35	22.78	44.97	76.18
9	1.0	5.4	0.5	3.95	0.4	48.58	67.04	95.53
10	2.0	9.4	1.5	1.63	0.2	21.68	47.23	67.77
11	1.5	7.4	1	2.15	0.25	27.34	50.03	80.04

Table 4: ANOVA results of the selected model.

Source	Sum of squares	df[a]	Mean square	F-value	*p*-value (Probe > F)	Regression coefficient
Content uniformity						
Model	1.80	2	1.80	75.12	<0.0001	0.7886
Paddle rotation time	1.45	1	1.45	136.19	0.0968	-
Lack of fit	0.054	6	0.033	1.93	0.1043	-
Friability						
Model	0.3816	2	0.1908	9.46	0.0078	0.6144
Pre-compression force	0.1074	1	0.1074	5.32	0.0510	-
Lack of fit	0.1581	6	0.0264	16.45	0.0584	-
Dissolution (1 hr)						
Model	0.9514	1	0.9514	288.84	<0.0001	0.7378
Main-compression force	0.9514	1	0.9514	288.84	<0.0001	-
Lack of fit	0.0263	8	0.0033	1.27	0.5018	-
Dissolution (3 hr)						
Model	0.3277	1	0.3277	258.03	<0.0001	0.7855
Main-compression force	0.3277	1	0.3277	258.03	<0.0001	-
Lack of fit	0.0102	8	0.0013	16.45	0.0584	-
Dissolution (8 hr)						
Model	0.1675	1	0.1675	40.31	0.0002	0.8487
Main-compression force	0.1675	1	0.1675	40.31	0.0002	-
Lack of fit	0.0332	8	0.0042	4.91	0.1739	-

[a]degrees of freedom.

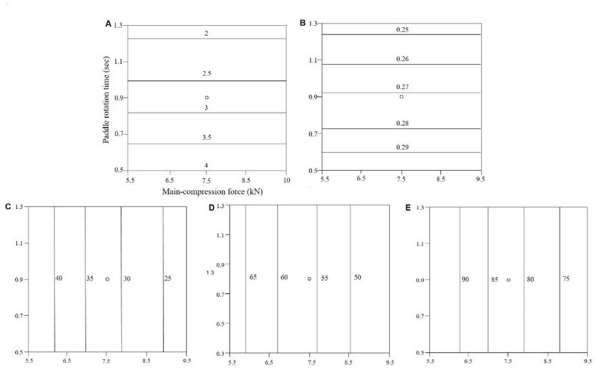

Figure 1: Main effect of paddle rotation time and main-compression forces on (A) content uniformity, (B) friability, (C) dissolution (1 hr), (D) dissolution (3 hr), and (E) dissolution (8 hr) at pre-compression force (1.5 kN). ○; center points (*n*=3).

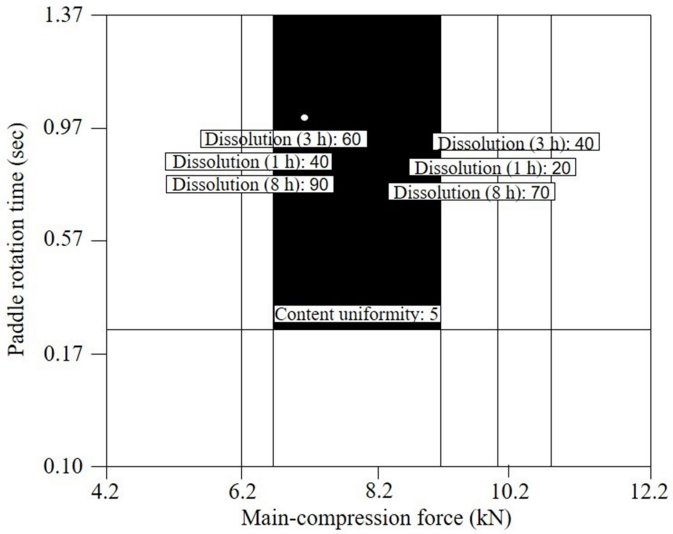

Figure 2: Design space for tablet compression process on the ivabradine sustained release tablet at pre-compression force (1.5 kN). ○; center points (*n*=3).

DISCUSSION

The goal of the tablet compression process DoE for the critical material attributes (CMA) and critical process parameters (CPP) is to confirm the robustness of ivabradine SR tablets using three factors (pre- and main-compression forces and paddle rotation time). A QbD approach is applied to optimize the initially developed formulation and manufacturing process based on brainstorming of the team and past experience.[14,15] The process of QbD is as follows: (1) defining Quality Target Product Profile (QTPP), (2) defining CQAs, (3) identifying the initial risk assessment, (4) setting up DoE based on high-risk factors in the initial RA, and (5) determining the DS, which is derived from the ranges of responses as CQAs. Finally, (6) determining a control strategy.[12]

In this study, the initial risk assessments of the tablet compression process were established as low, medium, or high risk, considering CQAs (Table 1). QTPP influenced by CQAs of ivabradine SR tablets was established based on a reference drug (Procoralan®).[12] Generally, feed speed, precompression force, main compression force, turret speed, press, and compression run time can be factors in the tablet compression process for the DoE study.[16] In this study, the factors (pre- and main-compression force and paddle rotation time) for the tablet compression process constituted the DoE because these factors can affect the product CQAs of content uniformity, friability, and dissolution (Table 2).

The results for all responses are shown in Table 3, and the results were analyzed through ANOVA using Design Expert software version 13.0.5.0 (Table 4). The main compression force of the ivabradine SR tablet had a strong influence on dissolution, except for two factors (precompression and paddle rotation time) (Table 4). Additionally, the various effects of the factors are shown in Figure 1. Figure 1A shows that none of the factors had an important effect on the content uniformity of tablet compression. The results of the content uniformity between 1.31% and 4.09% were also found to be not significant (Table 3). However, a lower paddle rotation time may increase the content uniformity of the tablet (Figure 1A). The results of the friability between 0.20% and 0.40% were also found to be not significant (Table 3). However, the pre-compression force had a minimally significant effect (p=0.051) (Table 4). As shown in Figure 1B, a lower pre-compression force may increase the friability of the tablet. The main compression force had a significant effect (1 hr, p<0.0001; 3 hr, p<0.0001; and 8 hr, p=0.0002) on tablet dissolution (Table 4). Figure 1(C, D, and E) shows that the main compression force had a significant effect on the dissolution (1, 3, and 8 hr) of the tableting process. First, the main effect indicated that a decrease in the main compression force may have increased the dissolution rate at 1 and 3 hr. Batches 2, 7, and 9 resulted in unacceptable ranges (46.65, 44.16, and 48.58) of dissolution rate (1 hr) based on the acceptance criteria (20.0-40.0%) (Table 3). Batches 1, 2, 7, and 9 also resulted in unacceptable ranges (65.42, 69.58, 69.86, and 67.04) of dissolution rate (3 hr) based on the acceptance criteria (40.0-60.0%) (Table 3). Second, the main effect indicated that an increase in the main compression force may have decreased the dissolution rate at 8 hr. Batches 4, 5, 6, 8, and 10 also resulted in unacceptable dissolution rates (78.45, 62.56, 79.94, 76.18, and 67.77) of dissolution rate (8 hr) based on the acceptance criteria (≥80.0) (Table 3). This result indicates that the main compression force can affect the dissolution, hardness, and friability.[16] The main compression force strongly affected dissolution. Content uniformity can also be slightly affected by the paddle rotation time.

In general, if the regression coefficient (R^2) value is 0.7 or higher, the DS can be established.[17,18] Our results showed that the values of R^2 for content uniformity, friability, and dissolution (1, 3, and 8 hr) were 0.7886, 0.6144, 0.7378, 0.7855, and 0.8487, respectively (Table 4). According to the results in Table 3, the DS was fitted to

the tableting process with respect to content uniformity, friability, and dissolution. To ensure the robustness of the tableting process, the DS (95% confidence interval) is shown in Figure 2.[19] The white area indicates that the goal of the response was not reached. The optimal range is indicated by the black area. If the paddle rotation time and pre- and main-compression forces are produced at approximately 0.27–1.37 s, 1.5 kN, and 7.7–9.2 kN, the desired content uniformity, friability, and dissolution rate of tablets will be obtained. The CS was established by the DS, and the values of three factors (paddle rotation time and pre- and main-compression forces) were identified as 0.7 s, 1.5 kN, and 8 kN, which are representative of good processes for all responses.[15,20] This study aimed to optimize the drug product tablet compression process and reduce the risk of failure. The initial risks of the tablet compression process were updated according to the DoE results.

CONCLUSION

The robust ranges in the tableting process for ivabradine SR tablets were identified using a DS through responses. We identified that the dissolution was highly affected by the main compression force. Content uniformity and friability were slightly affected by paddle rotation time and pre-compression force, respectively. Based on the results of this tableting DoE, the paddle rotation time (0.7 s) and pre- and main-compression forces (1.5 and 8 kN) for the tablet compression process were identified with optimal ranges for the acceptance criteria of content uniformity, friability, and dissolution.

ACKNOWLEDGEMENT

This work was (Partially) supported by the Brain Busan 21 Plus project in 2023.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

ABBREVIATIONS

SR: Sustained release; **CPP:** Critical process parameters; **DoE:** Design of experiments; **QTPP:** Quality target product profile; **DS:** Design space; **CQAs:** The Critical quality attributes; **QbD:** Quality by design; **CMAs:** Critical material attributes; **ANOVA:** Analysis of variance; **CS:** Control strategy.

SUMMARY

- Ivabradine SR tablet was investigated the ranges of tablet compression for drug product through design of experiments.
- Paddle rotation time (0.7 s) and pre- and main-compression forces (1.5 and 8 kN) were optimal ranges for drug product.
- The identification of the ranges for tablet compression will produce high quality products.

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Cite this article: Kim K. Tablet Compression Optimization of Ivabradine Sustained-Release Tablet Using Full Factorial Design. Indian J of Pharmaceutical Education and Research. 2024;58(3):730-5.