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Original Research Article

Optimization of ticagrelor tablet for gastro-retentive drug delivery using full factorial design

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Abstract

Purpose: *To identify the optimized region of formulation using quality by design for developing ticagrelor gastro-retentive (GR) tablets.*
Methods: *A 23 + 3 full factorial design of experiments study was used to identify three factors (polyethylene oxide (PEO), compression, and volume of granulating fluid) involved in the wet granulation and compression process of ticagrelor GR tablets. Hardness, friability, content, dosage unit uniformity, and pH 1.2 dissolution rate (at 4, 8, and 12 h) were evaluated as critical quality attributes via analysis of variance using Design Expert software.*
Results: *All seven models were significantly influenced based on analysis of variance results ($p < 0.05$). Hardness and friability were significantly affected by compression ($p < 0.0001$). Content uniformity was significantly affected by the interaction between compression and granulating water volume for wet granulation ($p < 0.05$), and dosage unit uniformity was significantly affected by the volume of granulating fluid for wet granulation ($p < 0.05$). However, all results were within acceptable ranges. Polyethylene oxide (PEO) (4 h, $p < 0.05$; 8 h, $p < 0.05$; 12 h, $p < 0.05$) and compression (4 h, $p < 0.05$; 8 h, $p < 0.05$; 12 h, $p < 0.05$) had negative effect on pH 1.2 dissolution rate.*
Conclusion: *Design of experiment (DoE) approach has been used to optimize region of PEO, compression, and volume of granulating fluid for formulation development. This outcome is expected to be a basis for further research to develop TCG GR tablets on a large production scale.*

Keywords: *Full-factorial design, Gastro-retentive drug delivery system, Optimization, Quality by design, Ticagrelor*

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INTRODUCTION

Ticagrelor (TCG), an antiplatelet agent, is used in treating acute coronary syndrome where it functions as a P2Y12 platelet adenosine diphosphate receptor antagonist [1]. It is classified as a BCS class Ⅳ drug owing to its low solubility and permeability, and its bioavailability after oral administration is approximately 36 % [1]. Based on previous studies, TCG absorption decreases further in the lower gastrointestinal tract (GIT) [2]. Mean half-life of TCG is 7.0 – 8.5 h and as a result it should be administered within this time [3]. The key to developing drug formulations with narrow absorption windows,

such as TCG, involves maintaining the dosage form in the stomach [4]. Gastro-retentive (GR) drug delivery systems (GRDDS) enable tablets to extend their retention time in the stomach and delay drug release [4]. They have several different systems, including high-density (sinking), low-density (floating), expandable, bio-adhesive, super porous hydrogel, and magnetic systems [4]. Quality by design (QbD) is a systematic approach that emphasizes the understanding of processes, products, and process control based on scientific approaches and quality risk management [5]. In contrast to previous quality testing systems based on trial and error, the QbD system is a pharmaceutical quality management system based on statistics [6]. The International Conference on Harmonization (ICH) published the ICH guidelines Q8 (R2), Q9, and Q10, called the Q-trio, and Q8, Q9, and Q10 questions and answers (R4) to emphasize the importance of QbD [6]. The quality target product profile, a characteristic that ensures quality, should be defined based on prior knowledge to perform QbD [7]. Critical quality attributes (CQA) that affect the quality target product profile should also be identified [7]. Critical material attributes (CMA) and critical process parameters (CPP) that affect CQA are selected via risk assessment (RA) [7]. With appropriate statistical tools such as design of experiment (DoE), the range to which selected factors affect quality must be identified and the derived region wherein the complete manufacturing process is achieved must be verified via deriving design space (DS). The DS is defined in ICH Q8 as the multidimensional combination and interaction of input variables (e.g., material attributes) and process parameters that have been demonstrated to provide assurance of quality [7]. Working within a DS was not considered a change; however, movement out of the DS was regarded as a change [8]. Ticagrelor GR tablets with expandable systems enhance drug absorption in the upper GIT and improve medication compliance [10]. This study aimed to develop a TCG GR tablet with an expandable system within a gastro-retentive drug delivery system (GRDDS), using polyethylene oxide (PEO) to enhance TCG bioavailability and improve medication compliance.

EXPERIMENTAL

Samples and reagents

Ticagrelor (TCG) was supplied by Honour Lab Ltd (Hyderabad, India). Microcrystalline cellulose (Avicel PH 101), hypromellose (Methocel E6 Premium LV), dicalcium phosphate, PEO (Polyox™ WSR N-60K), and magnesium stearate were purchased from Whawon Pharm Co Ltd, and Masung & Co Ltd (Seoul, South Korea). Acetonitrile, methanol, other chemicals, reagents, and solutions were purchased from Honeywell Burdick & Jackson (MI, USA).

TCG GR tablet formulation

All formulations (700 mg/tablet) were prepared by wet granulation (Table 1). Ticagrelor (Honour Lab Ltd, Hyderabad, India), microcrystalline cellulose (Avicel PH 101, Whawon Pharm Co. Ltd, Seoul, South Korea), and hypromellose (Methocel E6 Premium LV, Whawon Pharm Co., Ltd., Seoul, South Korea), were first mixed in plastic bags manually and granulated with purified water. The granules were dried at 70 ℃ for 30 min in a dry oven (OF-22GW, Jeio Tech, Daejeon, Korea), with a loss on drying approximately 1.5 %. Dried granules were milled using a No. 30 sieve (600 µm). After milling, dicalcium phosphate (Whawon Pharm Co. Ltd, Seoul, South Korea) and PEO (Polyox™ WSR N-60K Whawon Pharm Co., Ltd., Seoul, South Korea), were added to the granules. Finally, magnesium stearate (Whawon Pharm Co. Ltd, Seoul, South Korea) was mixed with the granules for lubrication. The mixture was compressed using a single-punch tablet machine (Autotab-200TR; Ichihashi Seiki Co., Ltd., Kyoto, Japan).

Table 1: Formulations for wet granulation of ticagrelor GR tablet

Ingredient	F1	F2	F3
	mg/tablet		
Ticagrelor	180	180	180
Hypromellose	80	80	80
Dicalcium phosphate	50	50	50
Microcrystalline cellulose	353	333	313
Polyethylene oxide	30	50	70
Magnesium stearate	7	7	7

Risk assessments

Risks of each factor in the formulation and manufacturing process were evaluated for their potential impact on CQA by conducting an initial RA. Failure mode effect analysis was used as a quality risk management tool to select factors that could affect CQA. Based on research experience and prior knowledge, the risk level was classified into low, medium, and high. Factors with high impact were selected [10].

A 2^3 + 3 full factorial design

Critical material attributes and critical process parameters, which are factors that may affect

CQA, were selected through an initial RA according to results of preliminary investigations. Based on initial RA results, the CMA was PEO, and CPP was the compression force and volume of granulating fluid. To confirm optimum conditions for the formulation of TCG GR tablets, 2^3 + 3 FFD was applied to verify the effect of CMA and CPP on formulation development using Design Expert software version 13 (Stat-Ease Inc., MN, USA) (Table 2). In this case, the independent variables were PEO, compression force, and volume of granulating fluid; the dependent variables were tablet hardness (Target: 6 – 14 kp), friability (Target: acceptance value (AV) ≤ 0.5 %), content (Target: 95.0 – 105.0 %), dosage unit uniformity (Target: AV ≤ 15 %), and dissolution rate (Target: within ≤ 15 % of target dissolution rate at 4 and 8 h, within ≤ 10 % of target dissolution rate at 12 h in pH 1.2 solution, and target dissolution rate (4 h = 30 %, 8 h = 60 %, 12 h = 80 %). Three levels were formulated (PEO (30, 50, and 70 mg), compression (600, 800, and 1000 kgf), and volume of granulating fluid (5, 6, and 7 mL). The upper conditions are listed in Table 2. Furthermore, three center points were added to the existing eight experimental points to check the curvature effect and reproducibility of the experiment (total number of experimental points was 11) (Table 3).

Loss on drying

Loss on drying was measured using a halogen moisture analyzer (MB90, Ohaus, Seoul, South Korea) exposed to 105 °C for 15 min.

Table 2: 2^3 + 3 full factorial design for DoE of TCG GR tablet manufacturing process

Factor			Level		
			-1	0	+1
CMA	X_1	Polyethylene oxide (mg)	30	50	70
CPP	X_2	Compression (kgf)	600	800	1000
	X_3	Volume of granulating fluid (ml)	5	6	7
Responses		**Goal**	**Acceptable ranges**		
Y_1	Hardness (kp)	Range	$6.0 \leq Y_1 \leq 14.0$		
Y_2	Friability (%)	Minimize	$Y_2 \leq 0.5$		
Y_3	Content (%)	Range	$95.0 \leq Y_3 \leq 105.0$		
Y_4	Uniformity of dosage units (AV*)	Minimize	$Y_4 \leq 15.0$		
Y_5	pH 1.2 dissolution rate at 4 h (%)	Range	$15.0 \leq Y_5 \leq 45.0$		
Y_6	pH 1.2 dissolution rate at 8 h (%)	Range	$45.0 \leq Y_6 \leq 75.0$		
Y_7	pH 1.2 dissolution rate at 12 h (%)	Range	$70.0 \leq Y_7 \leq 90.0$		

Table 3: Design of experiment (DoE) of 2^3+3 FFD to optimize TCG GR tablet manufacturing process

Batch No.	Factor: Material Attribute	Factor: Process Parameter		Responses						
	X_1: Polyethylene oxide	X_2: Compression	X_3: Volume of granulating fluid	Y_1: Hardness	Y_2: Friability	Y_3: Content	Y_4: Uniformity of dosage units	Y_5: pH 1.2 dissolution rate at 4 h	Y_6: pH 1.2 dissolution rate at 8 h	Y_7: pH 1.2 dissolution rate 12 h
	(mg)	(kgf)	(ml)	(kp)	(%)	(%)	(AV*)	(%)	(%)	(%)
1	30	600	5	11.8	0.11	100.99	3.40	34.60	65.92	78.12
2	70	1000	5	8.8	0.05	97.41	3.31	23.61	56.43	69.65
3	70	600	7	8.2	0.10	98.10	3.50	35.70	62.07	74.89
4	30	1000	7	8.8	0.06	100.96	0.79	34.23	61.38	75.76
5	70	1000	7	12.1	0.07	102.20	0.27	24.77	57.46	68.92
6	50	800	6	9.4	0.08	100.44	2.44	29.56	63.12	74.15
7	30	600	7	8.2	0.10	99.47	1.30	34.48	63.54	77.83
8	50	800	6	9.1	0.07	100.65	2.18	30.53	61.27	74.30
9	50	800	6	9.7	0.07	100.23	2.70	30.58	61.39	73.98
10	30	1000	5	12.7	0.06	98.59	2.88	35.91	63.57	76.42
11	70	600	5	5.3	0.12	100.72	0.49	35.39	58.57	75.21

Tablet hardness

Tablet hardness was tested using a hardness tester (Tablet Tester 8M, Dr. Schleuniger® Pharmatron, Ukraine). Three tablets were tested randomly from each batch and the average hardness was measured.

Friability

Friability was tested using a friability tester (FR 2000; Copley Scientific Limited, Nottingham, UK). Ten tablets from each batch were randomly weighed (W_1). The equipment was rotated at 25 rpm for 4 min, and the tablets were weighed again (W_2). The friability (F) percentage was determined using Eq 1.

$$F\ (\%) = \{(W_1 - W_2)/W_1\}100 \quad \ldots\ldots\ldots\ldots\ldots\ldots (1)$$

Content test

Content was evaluated at 240 nm using an Agilent 1100 Series HPLC system (Agilent Technologies, CA, USA). Mobile phase was a mixture of potassium dihydrogen phosphate buffer (Honeywell Burdick & Jackson (MI, USA) and acetonitrile (40:60, v/v) (Honeywell Burdick & Jackson (MI, USA), and the buffer pH was adjusted to 3.0 with phosphoric acid before mixing. A standard solution was prepared as follows: The TCG reference substance (27 mg) was placed in a volumetric flask and filled to the 100 mL mark with 40 % acetonitrile (acetonitrile and water, 40:60, v/v). The solution was stirred for 30 min at 500 rpm and filtered with a 0.45 µm RC filter (Sartorius AG, Goettingen, Germany).

Stock solutions were prepared as follows: Tablets were ground with a pestle and mortar. Ticagelor tablet powder (700 mg) and 50 mL diluent were added to a 100 mL volumetric flask. The solution was sonicated for 30 min using a sonicator (Power Sonic 520, Hwashin Tech Co., Ltd., South Korea) and stirred for 30 min at 500 rpm after filling up to the mark with diluent.

The sample solution was prepared as follows. Stock solution (15 mL) was diluted to 100 mL with the diluent and stirred for 30 min at 500 rpm. The solution was then filtered with a 0.45 µm RC filter.

Uniformity of dosage units

The uniformity of dosage units was determined by performing a content uniformity test. Ten tablets (10) were randomly tested from each batch and a content uniformity test was performed similar to the content test.

In vitro dissolution study

Dissolution test (triplicates for each batch) was performed in pH 1.2 buffer (900 mL, 37 ± 0.5 ℃) using the USP apparatus type 1 (basket method at 100 rpm). The dissolution samples were prepared by withdrawing 2 mL from each media in the vessel at 4, 8, and 12 h and filtrated with 0.45 µm RC filter. Equal amounts of fresh medium were added after each withdrawal. The samples were analyzed using an Agilent 1100 series HPLC system.

Data analysis

All data were analyzed with the statistical software (Design expert® Software Version 13, Stat-Ease Inc., USA) and two-way analysis of variance (ANOVA) was performed. $P < 0.05$ was considered statistically significant.

RESULTS

Tablet compression process variables

Results of the initial RA are summarized in Table 4. The risk level was set as high, and PEO quantity was selected as CMA. The risk level of compression was also set as high, and selected as CPP.

Design outcomes for CMA and CPP

The ANOVA results derived from the results in Table 3 are shown in Table 5. Results of Table 3 showed that hardness (kp) varied from 8.2 to 12.7, friability (%) from 0.05 to 0.11, content (%) from 97.41 to 102.20, uniformity of dosage units (AV) from 0.27 to 3.50, pH 1.2 and dissolution at 4 h (%) from 23.61 to 35.91, pH 1.2 and dissolution at 8 h (%) from 56.43 to 65.92, as well as pH 1.2 and dissolution at 12 h (%) from 68.92 to 78.12. In addition, the contour plots in Figure 1 show that all factors affected the response. Statistically significant models were indicated by $p < 0.05$. Models were deemed suitable when the p-value of the lack of fit was greater than 0.05.

Based on the ANOVA results, *p*-values of all models were less than 0.05, and p-values of all lack-of-fit models were greater than 0.05. Coefficient of determination (R^2) showed high values ($R^2 > 0.9$) in all models except for the content test.

Table 4: Initial risk assessment of tablet compression process variables

Drug Product CQA	Material Attribute				
	Microcrystalline Cellulose	**Hypromellose**	**Dicalcium phosphate**	**Polyethylene oxide**	**Magnesium stearate**
Hardness	Medium	Low	Low	Low	Low
Friability	Low	Low	Low	Low	Low
Content	Low	Low	Low	Low	Low
Uniformity of dosage units	Low	Low	Low	Low	Low
Dissolution	Low	Medium	Low	High	Low

Drug Product CQA	Process Parameter							
	Mixing & Wet granulation					**Tablet compression**		
	Mixing time	*Volume of granulating fluid*	***Drying***	***Screening***	***Final mixing & Lubricating***	***Pre compression***	***Compression***	***Feeder paddle speed***
Hardness	Low	Low	Low	Low	Low	Medium	High	Low
Friability	Low	Low	Low	Low	Low	Medium	High	Low
Content	Low	High	Low	Low	Low	Medium	Low	Medium
Uniformity of dosage units	Low	High	Low	Low	Low	Medium	Low	Medium
Dissolution	Low	Low	Low	Low	Low	Medium	High	Low

Table 5: ANOVA results of the 2^3+3 full factorial model

Response	Source	Sum of Squares	df	Mean Square	*P*-value	R^2
Hardness	Model	44.02	4	11.00	< 0.0001	0.9894
	A-PEO	6.30	1	6.30	0.0001	-
	B-Compression	9.90	1	9.90	< 0.0001	-
	AB	4.35	1	4.35	0.0003	-
	AC	23.46	1	23.46	< 0.0001	-
	Lack of Fit	0.2905	4	0.0726	0.6188	-
Friability	Model	0.0049	3	0.0016	0.0002	0.9332
	B-Compression	0.0045	1	0.0045	< 0.0001	-
	BC	0.0003	1	0.0003	0.0417	-
	Lack of Fit	0.0003	5	0.0001	0.4070	-
Content	Model	15.96	1	15.96	0.0003	0.7782
	BC	15.96	1	15.96	0.0003	-
	Lack of Fit	4.46	7	0.6374	0.0662	-
Uniformity of dosage units	Model	13.54	4	3.38	0.0011	0.9338
	C- volume of granulating fluid	2.23	1	2.23	0.0097	-
	AC	2.16	1	2.16	0.0104	-
	BC	4.56	1	4.56	0.0018	-
	ABC	4.59	1	4.59	0.0017	-
	Lack of Fit	0.8242	4	0.2060	0.2620	-
pH 1.2 dissolution rate at 4 h	Model	177.97	3	59.32	0.0002	0.9342
	A-PEO	48.76	1	48.76	0.0012	-
	B-Compression	58.59	1	58.59	0.0007	-
	AB	70.63	1	70.63	0.0004	-
	Lack of Fit	11.88	5	2.38	0.1267	-
pH 1.2 dissolution rate at 8 h	Model	75.60	3	25.20	0.0002	0.9295
	A-PEO	49.40	1	49.40	0.0001	-
	B-Compression	15.85	1	15.85	0.0032	-
	AC	10.35	1	10.35	0.0093	-
	Lack of Fit	3.59	5	0.7180	0.6897	-
pH 1.2 dissolution rate 12 h	Model	84.12	3	28.04	< 0.0001	0.9873
	A-PEO	47.34	1	47.34	< 0.0001	-
	B-Compression	29.26	1	29.26	< 0.0001	-
	AB	7.53	1	7.53	0.0002	-
	Lack of Fit	1.03	5	0.2065	0.1141	-

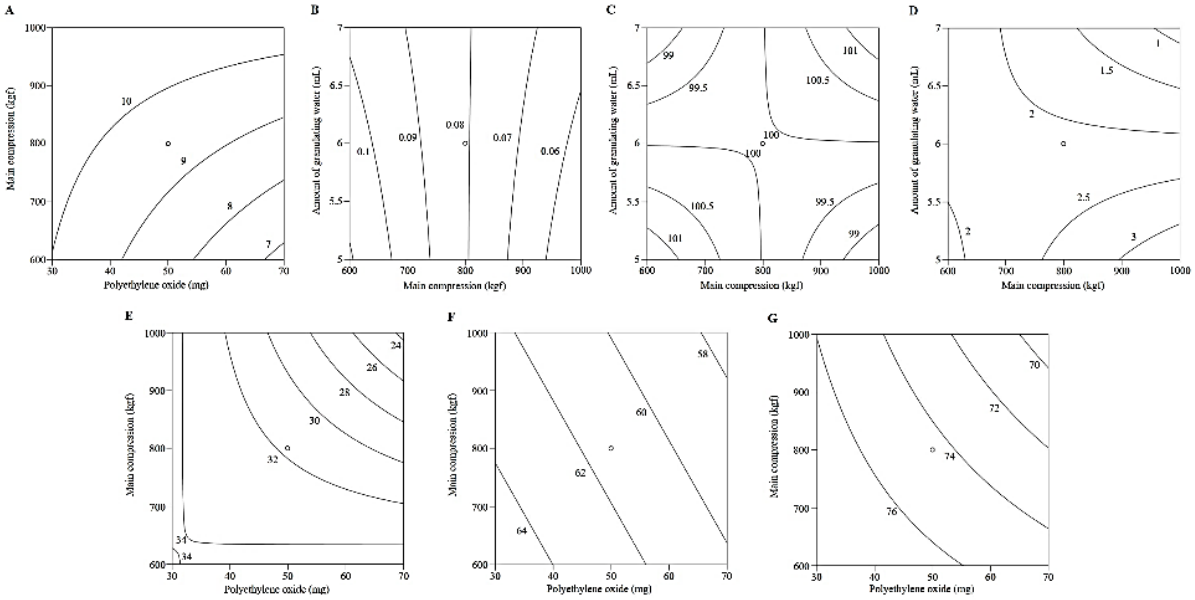

Figure 1: The main effect of polyethylene oxide, compression, and volume of granulating fluid on (A) hardness, (B) friability, (C) content, (D) uniformity of dosage units, (E) pH 1.2 dissolution rate at 4 h, (F) pH 1.2 dissolution rate at 8 h, and (G) pH 1.2 dissolution rate at 12 h. o indicates center points (n = 3)

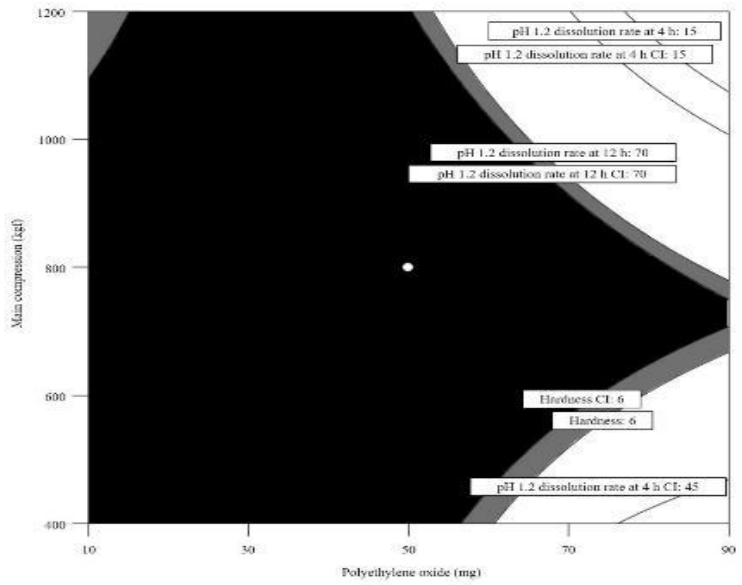

Figure 2: DS of the TCG GR tablet depending on polyethylene oxide and compression. o indicates center points (n = 3)

Optimization of TCG GR tablet CMA and CPP

To identify the robustness of the manufacturing process, the DS (95 % confidence interval) was derived. The optimized region was shown in black (Figure 2), and the white parts indicated that the results did not reach the target. The PEO range that satisfied the acceptable range of all dependent variables was 10.0 – 56.5 mg, and the compression range was 400.0 – 1086.0 kgf. In this case, when the volume of granulating fluid was 5.35 – 9.95 mL, the ranges of the other two independent variables were satisfied.

DISCUSSION

Polyethylene oxide (A, p = 0.0001) and compression (B, p < 0.0001) were factors that affected hardness, including the interactions between AB (p = 0.0003) and AC (p < 0.0001). Polyethylene oxide (PEO) is a hydrophilic polymer that swells upon exposure to moisture, forming a gel layer outside the tablet, and

providing a controlled release mechanism [11]. Thus, variations in PEO quantity, which is a CQA, may potentially impact dissolution. As a result, the risk level was set as “high,” and PEO quantity was selected as CMA. Depending on the granulating water volume, uneven granule distribution may occur, affecting the content and dosage unit uniformity. The compression may affect hardness, friability, and dissolution depending on its force [12]. Hardness increased when PEO quantity was low and compression was high. In general, high compression reduces tablet porosity and deforms it, which increases hardness [12]. In this formulation, the microcrystalline cellulose quantity was increased as the quantity of PEO decreased. Microcrystalline cellulose is vulnerable to plastic deformation, and these particles are deformed into gaps between other particles during tablet compression, increasing adhesion [13].

Accordingly, this result showed that the hardness increased with the microcrystalline cellulose quantity when compression was high. Compression ($p < 0.0001$) and the interaction with BC ($p = 0.0417$) affected friability. As predicted in the contour plot (Figure 1), friability either increased or decreased with changes in compression force. In general, an increase in compression causes an increase in hardness and a decrease in friability [14]; however, other studies have shown that friability increases again at high compressive forces, although the hardness may remain stable. In this study, friability decreased as the compressive force increased, and all friability values were less than 1 %, which is generally regarded as a good value. As a result, friability was affected by change in hardness due to compression.

The interaction of BC ($p = 0.0003$) was the factor that affected drug content; however, all results were within the range, and no distinct effects were observed due to the level variation of independent variables. Thus, variation in independent variable levels had an impact on the content; though it was not significant (97.41 – 102.20 %). However, as the correlation is generally judged to be high when R^2 value is between 0.7 and 1.0, the content ($R^2 = 0.7782$) was also found to have a high correlation between variables [15]. The volume of granulating fluid ($p = 0.0097$) and interactions of AC ($p = 0.0104$), BC ($p = 0.0018$), and ABC ($p = 0.0017$) affected dosage unit uniformity. Similar to drug content, all results were within range and no distinct effects were observed and the impact on dosage unit uniformity was not significant.

Polyethylene oxide (PEO) (4 h, $p = 0.0012$; 8 h, $p = 0.0001$; 12 h, $p < 0.0001$), compression (4 h, $p = 0.0007$; 8 h, $p = 0.0032$; 12 h, $p < 0.0001$), and the interaction of AB (4 h, $p = 0.0004$; 12 h, $p = 0.0002$) and AC (8 h, $p = 0.0093$) had significant effects on dissolution of the tablets at pH 1.2. An increase in compression leads to a decrease in porosity and an increase in mechanical properties, and as a result, the dissolution rate may decrease [16]. Furthermore, when a tablet containing PEO is exposed to water, it begins to hydrate, expand, and form a gel layer outside the tablet core, which regulates water penetration into the tablet core and drug release [17].

The formation of a hydrogel layer involves three phases: expansion, maintenance, and corrosion. In the last phase, the PEO polymer chains begin to dissolve in the media [11]. Because of this phenomenon, water penetration is slow, while drug release decreases and is prolonged [17]. Other studies have shown that increasing the proportion of PEO in a formulation reduces dissolution [17]. In this study, an expandable system was applied using polyethylene oxide (PEO), a polymer that is widely used in controlled-release formulations. The expandable system was designed to expand the tablet to be larger than the pylorus diameter using polymers [18]. Hydration and expansion of PEO in the presence of water form a gel layer outside the tablet [11]. The formed gel layer is eroded as a result of water penetration and the drug is released through cracks in the eroded gel layer [11]. In this process, the drug release is controlled and delayed. Therefore, the expansion and dissolution processes controlled the drug dissolution rate according to the quantity of PEO.

CONCLUSION

This study is a laboratory-scale quality-by-design (QbD) study for commercialization. This study shows the optimized region of critical factors for manufacturing TCG GR tablets by identifying the tendency for CMA and CPP and is expected to be a basis for further research to develop TCG GR tablets on a large production scale.

DECLARATIONS

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Ethical approval

None provided.

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 associated with this work.

Contribution of Authors

We declare that this work was done by the authors named in this article and all liabilities pertaining to claims relating to the content of this article will be borne by the authors. Yong Seong Lee performed the experiments in this study. Kang Min Kim and Jae Seon Kang reviewed the manuscript and provided comments on the study design. Kang Min Kim and Jae Sung Pyo drafted the manuscript and supervised the study.

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