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Optimization of gemifloxacin immediate-release tablets using quality by design

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Abstract

The objective of this study is to determine the design space (DS) for a dissolution-enhanced gemifloxacin immediate-release (IR) tablet incorporating hydroxypropyl-β-cyclodextrin (HPCD) for improved solubility, utilizing a quality by design (QbD) approach. Based on the preliminary studies, hardness, friability, disintegration time, assay, content uniformity, and dissolution rate were identified as the critical quality attributes (CQAs) for optimization. Through the initial risk assessment, crospovidone, main compression force, and the amount of granulating fluid were identified as factors influencing the CQAs, and a $2^3 + 3$ full factorial design of experiments (DoE) was conducted for optimization. According to the analysis of variance (ANOVA), both main compression force ($p = 0.004$) and the amount of granulating fluid ($p = 0.001$) significantly affected hardness. While the amount of granulating fluid was established as a primary factor influencing disintegration time ($p = 0.001$) and dissolution rate ($p = 0.006$). The other factors did not show a statistically significant impact on the remaining CQAs. The optimized ranges obtained from this study were as follows: crospovidone, 5.72–7.99%; main compression force, 1707.5–2372.3 kgf; and amount of granulating fluid, 5.36–6.12 mL. A $2^3 + 3$ full-factorial design of experiments (DoE) was applied to determine the relationship between independent and dependent variables, and a high-quality IR tablet meeting all predefined CQA criteria [hardness (18.0–22.0 kp), friability (≤0.5%), disintegration time (16.0–20.0 min), assay (95.0–105.0%), content uniformity (AV ≤ 5), and dissolution similarity ($f_2 \geq 50$)] was developed through the systematic optimization of formulation and manufacturing processes.

Keywords: Gemifloxacin, Pharmaceutical preparations, Quality control

1. Introduction

Tablets are the most common and traditional dosage form in the pharmaceutical industry due to their high patient convenience and cost-effective production [1]. Because of these characteristics, tablets significantly contribute to improving patient compliance [2]. Gemifloxacin is a fourth-generation fluoroquinolone antibiotic, and its molecular structure plays a crucial role in its antibacterial activity. The drug contains a cyclopropyl ring at the N1 position and a fluorine atom at the C6 position on the quinolone backbone. These structural features enable a broad antibacterial spectrum and potent efficacy [3]. The presence of a pyrrolidinyl substituent at the C7 position has been shown to enhance antibacterial activity against gram-positive bacteria [4]. Gemifloxacin's chemical structure allows it to target both DNA gyrase and topoisomerase IV, two enzymes critical for bacterial survival. By inhibiting these enzymes, it interferes with DNA replication, transcription, and repair, ultimately leading to bacterial cell death [5,6]. Based on these structural and mechanistic advantages, gemifloxacin is clinically used for the treatment of various bacterial infections. Its primary therapeutic indications are community-acquired pneumonia (CAP) and acute bacterial sinusitis (ABS) [7,8]. The pyrroline substituent at the C7 position enhances antimicrobial efficacy against gram-positive

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bacteria [9]. Gemifloxacin exhibits pH-dependent solubility owing to its zwitterionic nature, which limits its dissolution rate in the gastrointestinal tract and consequently reduces its oral bioavailability [4]. This poor aqueous solubility presents a significant challenge for the development of an effective oral solid dosage form. The formation of a stable 1:1 inclusion complex between gemifloxacin and hydroxypropyl-β-cyclodextrin (HPCD) has been confirmed by spectroscopic and molecular modeling approaches [10]. HPCD has been widely reported to improve the solubility, dissolution rate, and biological membrane permeability of quinolone-class antibiotics through inclusion complex formation [11]. Quality by Design (QbD) is a systematic approach to pharmaceutical development that emphasizes a thorough understanding of the product and its manufacturing process, rooted in scientific knowledge and quality risk management [12]. Over the years, QbD in the pharmaceutical field has evolved alongside the issuance of key guidelines from the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH), including ICH Q8 (Pharmaceutical development), ICH Q9 (Quality risk management), and ICH Q10 (Pharmaceutical quality system) [13]. The US Food and Drug Administration (FDA) encourages risk-based approaches and the adoption of QbD principles in drug product development, manufacturing, and regulation [14]. To apply QbD, the process begins by defining the quality target product profile (QTPP) to ensure the safety and efficacy of the drug product and to achieve the desired quality. For the accurate characterization of the QTPP, critical quality attribute (CQA) must be selected [15]. Critical material attribute (CMA) and critical process parameter (CPP) are selected for their primary influence on the CQA [14]. Using the selected variables, design of experiments (DoE) is performed to model the mathematical relationship between input and output variables, thereby defining the design space (DS) [16]. In this study, a DoE was performed using a $2^2 + 3$ full factorial design (FFD), and the solubilized gemifloxacin IR tablet was optimized based on the derived DS. The use of HPCD as a solubilizing agent in this formulation is based on its well-established ability to form inclusion complexes with poorly soluble drugs, thereby improving aqueous solubility and dissolution rate [11]. The solubility and bioavailability enhancement of the HPCD–gemifloxacin formulation, including in vitro solubility characterization and in vivo pharmacokinetic evaluation, have been investigated in a companion study currently in press for publication elsewhere [17]. Based on these findings, the gemifloxacin dose in the present formulation was set at 298.47 mg/tablet, reduced from the 320 mg dose of the reference product Factive®, with the aim of achieving equivalent therapeutic efficacy at a lower drug load. The present study therefore focuses on the formulation development and DoE-based optimization of the HPCD-solubilized gemifloxacin IR tablet to ensure consistent dissolution performance.

2. Materials and methods

2.1. Samples and reagents

Gemifloxacin was supplied by Sigma–Aldrich (St. Louis, MO, USA). Anhydrous silicon dioxide, microcrystalline cellulose (MCC, Avicel PH 101), crospovidone and magnesium stearate were purchased from Whawon Pharm Co., Ltd. (Seoul, South Korea). Hydroxypropyl-β-cyclodextrin (HPCD) was purchased from Roquette (Lestrem, France). Acetonitrile and monobasic sodium phosphate were purchased from Samchun Chemical Co., Ltd. (Seoul, South Korea). Formic acid was purchased from Junsei Chemical Co., Ltd. (Tokyo, Japan). For the comparative dissolution test, the reference tablet was Factive® (Gemifloxacin 320 mg) from LG Chem., Ltd.

2.2. Manufacture of gemifloxacin tablets

Gemifloxacin IR tablets were manufactured using the wet granulation method, with water employed as the granulating fluid. First, gemifloxacin (298.47 mg/tablet) was sieved through a 600 μm screen to prevent agglomeration. Then, HPCD (57.43 mg/tablet) and MCC 101 were added, followed by thorough mixing. The mixture was granulated uniformly by the addition of water. The wet granules were dried in a 70 °C drying oven (OF-22GW, Jeio Tech, Daejeon, Korea) until the loss on drying (LOD) was below 3%. The dried granules were passed through an 850 μm sieve and then blended with crospovidone and anhydrous silicon dioxide (9.40 mg/tablet). Magnesium stearate (4.70 mg/tablet) was added to improve the flowability of the granules and lubrication during tableting. As a CMA, crospovidone was incorporated at the predetermined percentage for each batch obtained through the DoE. Accordingly, the amount of MCC 101 was also adjusted. Tablets, each weighing 470 mg, were compressed using a single-punch tablet machine (Autotab-200TR, Ichihashi Seiki Co., Japan).

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2.3. Quality target product profile and critical quality attributes

The quality target product profile (QTPP) for the gemifloxacin IR tablet was defined based on the reference product (Factive®) and regulatory guidelines. A high-quality IR tablet in this study was defined as one satisfying all of the following CQA criteria: hardness of 18.0–22.0 kp, friability of ≤0.5%, disintegration time of 16.0–20.0 min, assay of 95.0–105.0%, content uniformity (AV) of ≤5, and dissolution similarity ($f_2 \geq 50$) with the reference product at pH 4.5.

2.4. Risk assessments and DoE

An initial risk assessment was performed to evaluate the impact of each formulation and manufacturing factor on the CQA. Through failure mode and effects analysis (FMEA), risk factors were identified and classified as 'low', 'medium', or 'high' based on prior knowledge.

Optimization studies were conducted on the CMA (Crospovidone) and CPPs (Main compression force and amount of granulating fluid), which were identified as high-risk factors through the initial risk assessment. The factor levels and responses for the optimization study are summarized in Table 1. This study was conducted employing a $2^3 + 3$ FFD using Design Expert software version 13 (Stat-Ease Inc.). Consequently, a total of 11 experiments were performed, comprising 8 factorial points and 3 center points to detect the curvature effect.

2.5. Hardness

The hardness of tablets was measured using a hardness tester (TBH 325, Erweka GmbH). Three tablets were randomly taken from each batch, and their mean value was recorded.

2.6. Friability test

Select the tablet that is the nearest to 470 mg, and measure the weight of 10 tablets. Using the measured tablets, friability testing was performed with a friability tester (FR 2000, Copley) operated at 25 rpm for 100 rotations. After the test is completed, reweigh the tablets and calculate the result using the following formula:

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

W1 is the weight of 10 tablets before the friability test, and W2 is the reweighed value of the same 10 tablets after the test.

2.7. Disintegration time

A disintegration tester (KDIT 200, Kukje Engineering Co.) was used to determine the disintegration time of the tablets. Distilled water maintained at 37 ± 2 °C was used as the medium, and the time for complete tablet disintegration was evaluated in seconds.

2.8. Estimation of drug content

The drug content and content uniformity were measured using a Shimadzu LC20 HPLC system (Shimadzu, Kyoto, Japan), with detection at a wavelength of 272 nm. The mobile phase of 20% acetonitrile containing 0.01% trifluoroacetic acid was used. The solution was prepared by dissolving 13.8 g of monobasic sodium phosphate in 100 mL of purified water, of which 80 mL was mixed with 720 mL of purified water and 200 mL of acetonitrile. This solution was used as the diluent for sample and standard preparations.

The standard solution of gemifloxacin was prepared as follows: Accurately weigh 17.0 mg of

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

Factor			Level		
			−1	0	+1
CMA	A	Crospovidone (%)	2	5	8
CPP	B	Main compression force (kgf)	1500	2000	2500
	C	Amount of granulating fluid (mL)	5	6	7

Response		Goal	Acceptable ranges
Y_1	Hardness (kp)	In range	$18.0 \leq Y_1 \leq 22.0$
Y_2	Friability (%)	Minimize	$Y_2 \leq 0.5$
Y_3	Disintegration (min)	In range	$16.0 \leq Y_3 \leq 20.0$
Y_4	Assay of gemifloxacin (%)	In range	$95.0 \leq Y_4 \leq 105.0$
Y_5	Uniformity of dosage units of gemifloxacin (AV)	Minimize	$Y_5 \leq 5$
Y_6	f_2 value of gemifloxacin in pH 4.5 (f_2 value at 10, 15, 30, 45, 60)	Maximize	$Y_6 \geq 50$

AV: Acceptance Value. kgf: kilogram-force. kp: kilopond.

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gemifloxacin reference standard and transfer it into a 100 mL volumetric flask. Add the diluent to approximately 70% of the flask volume and sonicate for 30 min. After sonication, fill to the calibration mark with the diluent, and filter the solution through a 0.45 μm RC filter (Sartorius AG, Goettingen, Germany). The resulting solution was used as the standard. The sample stock solution of Gemifloxacin was prepared as follows: More than 20 tablets were finely pulverized, and 267.7 mg of the powder was transferred to a 100 mL volumetric flask. The flask was filled to 70% with diluent, shaken for 15 min, and sonicated for 30 min. The volume was then adjusted to the mark with diluent. The sample solution of gemifloxacin was prepared as follows: Five milliliters of the stock solution were transferred to a 50 mL volumetric flask, and the volume was adjusted to the mark with diluent. Filter this solution through a 0.45 μm RC filter (Sartorius AG, Goettingen, Germany), and then use it as the sample solution. The content uniformity test was performed by analyzing ten individual samples. The acceptance value (AV) must be less than 15 to indicate uniformity.

2.9. Dissolution test

The dissolution test was conducted in 900 mL of pH 1.2, 4.5 and 6.8 buffer dissolution medium using USP apparatus 2 (paddle method, 50 rpm). Samples (2 mL) were withdrawn at specific times (10, 15, 30, 45, and 60 min) and filtered through a 0.45 μm RC filter (Sartorius AG, Goettingen, Germany) before analysis. The samples were analyzed using the previously described HPLC method.

2.10. Statistical analysis

All statistical analyses were performed using Design Expert® software version 13 (Stat-Ease Inc., Minneapolis, MN, USA). ANOVA was conducted to assess the statistical significance of each factor, with $p < 0.05$ considered statistically significant. Model adequacy was evaluated using the lack-of-fit test ($p > 0.05$) and the coefficient of determination ($R^2 > 0.7$). Dissolution similarity between the optimized formulation and the reference product (Factive®) was assessed using the similarity factor f_2, with $f_2 \geq 50$ indicating dissolution similarity, in accordance with FDA and EMA guidance.

3. Result

3.1. Initial risk assessment of gemifloxacin immediate-release tablet

In order to optimize the formulation and manufacturing process of gemifloxacin IR tablets, an initial risk assessment was conducted based on prior knowledge and preliminary experiments. The initial risk assessment was categorized into “low”, “medium”, and “high”, which were then summarized in Table 3. IR tablets are required to rapidly disintegrate and dissolve in the gastrointestinal tract after administration, ensuring a quick onset of action and bioavailability of the drug [18]. To achieve this performance, both crospovidone and the main compression force are crucial. Crospovidone, as a superdisintegrant, exhibits porous particle characteristics that enable rapid water absorption, significantly influencing the dissolution rate [19]. Therefore, it was evaluated as “high”. The main compression force influences the tablet porosity and interparticle bonding, thereby significantly affecting hardness, friability, disintegration time, and dissolution rate [20]. Therefore, it was classified as “high”. Furthermore, the amount of granulating fluid was classified as “high” because it significantly affects particle size and the generation of fines [21].

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

Batch No.	Factors: Material Attribute	Factor: Process Parameter		Responses					
	A	B	C	Y_1	Y_2	Y_3	Y_4	Y_5	Y_6
	(%)	(kgf)	(mL)	(kp)	(%)	(min)	(%)	(AV)	(f_2)
1	8	2500	7	15.03	0.16	23.14	100.95	0.74	37.86
2	8	1500	7	15.06	0.11	23.92	101.98	1.87	44.30
3	2	1500	5	20.84	0.14	17.88	100.48	1.29	51.96
4	5	2000	6	19.20	0.08	19.41	101.63	1.40	64.83
5	2	2500	5	26.82	0.07	18.51	100.68	2.75	51.42
6	5	2000	6	21.56	0.11	16.10	98.13	0.81	57.02
7	8	2500	5	26.15	0.09	16.15	100.30	0.43	64.11
8	5	2000	6	19.83	0.09	19.01	99.97	0.71	61.90
9	2	1500	7	12.11	0.11	23.41	99.05	2.21	33.07
10	8	1500	5	18.61	0.09	12.15	99.43	0.74	66.03
11	2	2500	7	20.29	0.09	23.32	100.76	0.88	23.14

AV: Acceptance Value. kgf: kilogram-force. kp: kilopond.

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

Material and process variables	Drug Product CQA					
	Hardness	Friability	Disintegration	Assay	Content uniformity	Dissolution
Hydroxypropyl-β-cyclodextrin	Low	Low	High	Low	Low	High
Microcrystalline cellulose 101	Low	Low	Low	Low	Low	High
Anhydrous silicon dioxide	Low	Low	High	Low	Low	High
Crospovidone	Low	Low	Low	Low	Low	Low
Magnesium stearate	Low	Low	Low	Low	Low	Low
Mixing & wet granulation	High	High	High	Low	Low	High
Pre-compression	Low	Low	Low	Low	Low	Low
Main compression force	High	High	High	Medium	Medium	High

3.2. DoE for formulation optimization

The DoE study was implemented to optimize the CMA (Crospovidone) and CPPs (Main compression force and amount of granulating fluid) identified through the initial risk assessment. A 2^3+3 full factorial design, including three replicated center points, was employed to detect curvature effects and improve the robustness of the experimental results. Table 3 summarizes the specific factor settings and the measured responses for each batch. The experimental results showed that the tablet hardness ranged from 15.03 to 26.15 kp, and the friability was measured between 0.09 and 0.41%. It was observed that the hardness of several batches deviated significantly from the acceptable range (16–20 kp). In the disintegration test, the results ranged from 12.15 to 23.92 min, and many batches deviated from the acceptable range (16–20 min). The assay results ranged from 98.13 to 101.98%, and the content uniformity results ranged from 0.43 to 2.21. All batches were confirmed to meet the acceptance criteria for both assay and content uniformity. In the dissolution test conducted for 60 min in a pH 4.5 medium, the f_2 values ranged from 23.14 to 66.03. It was observed that several batches were below the acceptable range ($f_2 \geq 50$).

3.3. Result of ANOVA, DS, and updated risk assessment

The repeated experimental results at the center points (batches 4, 6, and 8) presented in Table 2 were consistent, and the absence of curvature effect demonstrated the reliability of the DoE results. Based on the results presented in Table 3, ANOVA was performed, and the results are summarized in Table 4. A *p*-value less than 0.05 indicated a statistically significant effect, while a lack-of-fit *p*-value greater than 0.05 suggested that the model was appropriate. The Coefficient of Determination (R^2) is a measure of how well the model explains the data, and when it is above 0.7, the prediction results can be considered reliable. Fig. 1 presents six contour plots showing the effects of the main factors (A: Crospovidone, B: Main compression force, and C: Amount of granulating fluid) on each CQA. In the hardness test, B-Main compression force ($p = 0.004$) and C-Amount of granulating fluid

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

Response	Source	Sum of squares	df	Mean square	F-value	*p*-value	R^2
Hardness	Model	170.67	2	85.34	23.54	0.004	0.8548
	B	58.70	1	58.70	16.19	0.004	
	C	111.98	1	111.98	30.89	0.001	
	Lack of fit	26.01	6	4.34	2.90	0.278	
Friability	Model	0.0062	6	0.0010	4.53	0.083	0.8718
	Lack of fit	0.0004	2	0.0002	0.94	0.516	
Disintegration	Model	105.85	1	105.85	25.56	0.001	0.7396
	C	105.85	1	105.85	25.56	0.001	
	Lack of fit	30.74	7	4.39	1.35	0.490	
Assay	Model	5.76	7	0.8234	0.3646	0.877	0.4597
	Lack of fit	0.65	1	0.6451	0.2105	0.691	
Content uniformity	Model	1.87	3	0.6245	1.24	0.365	0.3473
	Lack of fit	3.24	5	0.6485	4.66	0.186	
Dissolution	Model	1523.30	3	507.77	6.65	0.019	0.7403
	C	1131.69	1	1131.69	14.82	0.006	
	Lack of fit	503.36	5	100.67	6.47	0.139	

df: degrees of freedom. R^2: coefficient of determination.

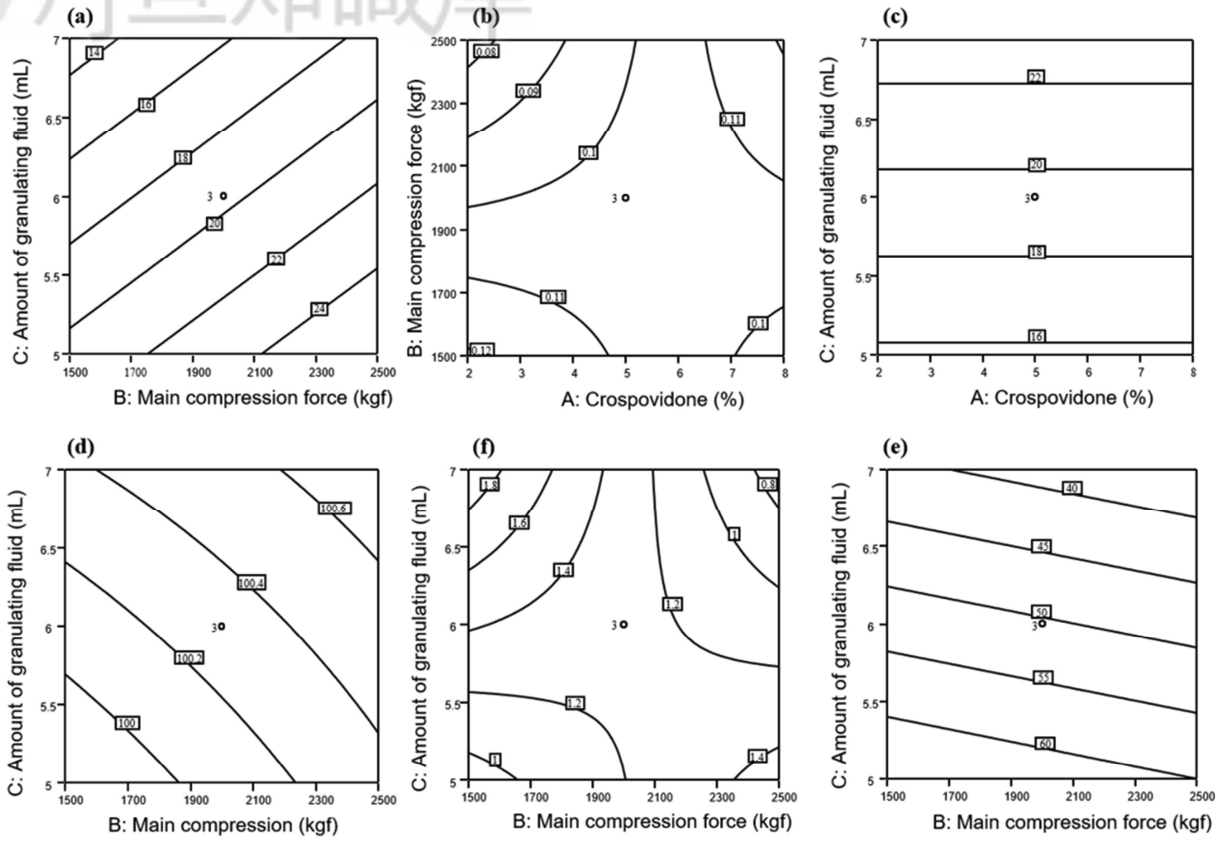


Fig. 1. Contour plots derived from the 2^3+3 full factorial DoE, showing the main effects of (A) crospovidone (%), (B) main compression force (kgf), and (C) amount of granulating fluid (mL) on each CQA: (a) hardness (kp), (b) friability (%), (c) disintegration time (min), (d) assay (%), (e) content uniformity (AV), and (f) dissolution similarity (f_2 value) at pH 4.5. Dashed lines indicate the predefined acceptable ranges for each CQA. ○; center points (n = 3).

($p = 0.001$) were identified as the main influencing factors, while no interaction was observed between the factors (Fig. 1a). As shown in Fig. 1a, tablet hardness increased with increasing main compression force and decreasing amount of granulating fluid, ranging from approximately 15 kp to 27 kp across the experimental space. On the other hand, friability, which was within the acceptable range for all batches, was found to have no specific main effect factors (Fig. 1b). In the disintegration test, C-Amount of granulating fluid ($p = 0.001$) was identified as the main influencing factor, and no interaction was observed with other factors (Fig. 1c). In Fig. 1c, disintegration time decreased markedly as the amount of granulating fluid was reduced, with values ranging from approximately 12 to 24 min. Assay and content uniformity were consistently within the acceptable range for all batches, regardless of factor levels (Fig. 1d and e). Therefore, these CQAs were not significantly affected by any of the factors. Similar to the disintegration test, C-Amount of granulating fluid ($p = 0.001$) was identified as the main influencing factor in the pH 4.5 dissolution test, and no interaction was observed among the factors (Fig. 1f). In Fig. 1f, the f_2 value increased as the amount of granulating fluid decreased, reflecting the promotion of dissolution by fines generation at lower granulating fluid levels. A DoE study was conducted to optimize the formulation, and the DS derived from the study is shown in Fig. 2. In the DS, the black area represents the optimal range of CMAs and CPPs that satisfy the CQAs, while the white dots indicate the center points of three replicate experiments. In the DS, the optimal ranges of the factors were identified as follows: Crospovidone 5.72–7.99%, Main compression force 1707.5–2372.3 kgf, and Amount of granulating fluid 5.36–6.12 mL. Through these studies, high-risk CMA and CPPs influencing hardness, friability, assay, disintegration, content uniformity, and dissolution were optimized and updated to a lower risk level.

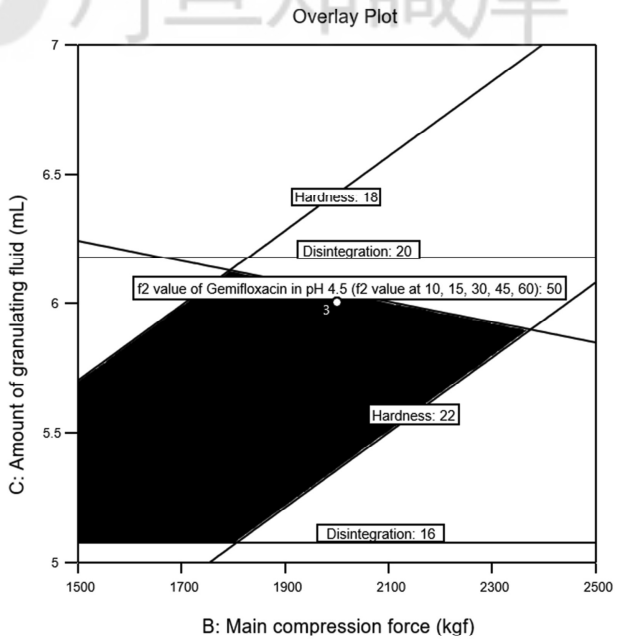


Fig. 2. Design space (DS) of the dissolution-enhanced gemifloxacin IR tablet as a function of main compression force (kgf) and amount of granulating fluid (mL), at a fixed crospovidone level of 6.86%. The black region represents the DS within which all predefined CQA criteria are simultaneously satisfied. ○; center points (n = 3).

3.4. Verification of the optimized formulation

To verify the validity and reliability of the derived DS, an optimized formulation was manufactured at the DS center point. This formulation was then evaluated for predefined CQAs and comparative dissolution testing to confirm compliance with all acceptance criteria. Specifically, the optimized formulation was prepared based on the DS presented in Section 3.3, using the center point conditions: 6.86% crospovidone, 2039.9 kgf main compression force, and 5.74 mL of granulating fluid. The optimized formulation was evaluated for predefined CQAs, demonstrating excellent properties with a hardness of 20.1 kp, friability of 0.11%, and a disintegration time of 17.9 min. In addition, the average assay was 100.4% and the content uniformity (AV) was 0.87, confirming that all acceptance criteria were fully satisfied. In comparative dissolution testing with the reference product Factive®, the f_2 values ranged from 64.49 to 88.73 across all dissolution media (pH 1.2, 4.5, and 6.8), demonstrating a high degree of similarity exceeding the acceptance criterion ($f_2 \geq 50$).

4. Discussion

The formulation and manufacturing process of the gemifloxacin IR tablet with improved dissolution, utilizing HPCD as a solubilizing agent, were optimized using DoE. DoE has been widely used to determine how multidimensional factors and their interactions influence the output responses of pharmaceutical products [22]. As shown in Table 4, the main effect factors for hardness were B-Main compression force ($p = 0.004$) and C-Amount of granulating fluid ($p = 0.001$). The main compression force is a representative factor influencing the tablet hardness. As the main compression force increases, the tablet porosity decreases, resulting in a stronger mechanical strength of the tablet [20]. In addition, an increase in the main compression force enhances the interparticle bonding within the tablet, leading to higher hardness values [23]. The amount of granulating fluid is a critical factor determining the formation of fines, granule size, and the mechanical strength of granules during wet granulation. When the amount of granulating fluid is insufficient, fines are generated, which increase the contact area between particles, thereby enhancing the interparticulate bonding and consequently increasing the tablet hardness [21,24]. As shown in Fig. 1a, tablet hardness tended to increase with an increase in main compression force and a decrease in the amount of granulating fluid. Generally, tablet friability depends on the compression force and tends to be inversely related to hardness. However, in this study, no significant factors affecting friability were observed. As shown in Table 3, the friability was in the range of 0.07–0.16%, all within the acceptable range. This indicates that the established formulation and process were robust across all levels of factors. In the disintegration test, the C-amount of granulating fluid was identified as a main influencing factor. As mentioned earlier, the amount of granulating fluid has a significant effect on the properties of the granules. A larger amount of water enhances the internal bonding strength of the granules, which can delay the disintegration time [25]. Conversely, when a smaller amount of granulating fluid is used, fine particles are generated. Compared with larger granules, these fine particles have a higher specific surface area, which accelerates water penetration through the pores within the tablet, and form weaker granules. Both mechanisms contribute to shortening the disintegration time [26]. Furthermore, crospovidone, as a superdisintegrant, can enhance the porosity of tablets and promote disintegration by absorbing water into the tablet through capillary action. However, according to the results presented in Table 3, crospovidone appears to have no significant effect on the disintegration time [19]. Fig. 1c clearly demonstrates that among the

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investigated variables, only the amount of granulating fluid had a significant effect on the disintegration time. A trend of decreasing disintegration time was observed corresponding to a decrease in the amount of granulating fluid. According to Table 2, both the assay (99.05–101.98%) and content uniformity (0.43–2.21%) were within the acceptable range, and no significant factors were identified. The assay and content uniformity are mainly influenced during the transfer of granules from the feeder to the die, which is largely dependent on the flowability of the granules. If the amount of granulating liquid during wet granulation is insufficient, a larger amount of fines is generated, which increases the specific surface area. Consequently, van der Waals and electrostatic forces between particles become stronger. As a result, the particles agglomerate more easily, which decreases the flowability of the granules [27]. This can be explained by the relatively high proportion of gemifloxacin (63.50%) in each tablet, which provides robustness even in the presence of fines generation. As shown in Table 2, factor C-Amount of granulating fluid ($p = 0.006$) was identified as a main significant factor affecting the dissolution rate at pH 4.5. As illustrated in the contour plot (Fig. 1f), the f_2 value tended to increase as the amount of granulating fluid decreased to the −1 level. As mentioned above, a lower amount of granulating fluid during granulation results in increased fines formation, which promotes disintegration and consequently enhances the dissolution rate. Therefore, reducing the amount of granulating fluid accelerated the dissolution rate, thereby yielding a higher f_2 value. Fig. 2 illustrates DS for the dissolution-enhanced IR tablet of gemifloxacin with respect to CQAs such as hardness, friability, disintegration, assay, content uniformity, and dissolution. The crospovidone was not selected as a significant factor for any of the CQAs, indicating that it had little impact on formulation optimization. Therefore, Fig. 2 represents the DS defined by main compression force and the amount of granulating fluid. As shown in Fig. 2, the acceptable ranges of the selected CMA and CPP are relatively narrow. This indicates that the quality attributes are sensitive to subtle variations in formulation and process parameters, emphasizing the need for strict process control within the DS. To verify the validity of the established DS, an optimized formulation was prepared at the DS center point. It was subsequently evaluated for predefined CQAs and comparative dissolution testing. As a result, all CQAs met the predefined acceptance criteria, and the comparative dissolution test demonstrated a high degree of similarity exceeding the acceptance criterion ($f_2 \geq 50$) across all dissolution media (pH 1.2, 4.5, and 6.8). These results suggest that the established DS can reliably ensure consistent product quality in the actual manufacturing process. Overall, the development of the dissolution-enhanced gemifloxacin IR tablet was successfully accomplished using a DoE-based systematic formulation design strategy. In the wet granulation process, the amount of granulating fluid had a significant effect on hardness, friability, and f_2 value, while main compression force significantly affected hardness only, and the crospovidone did not have a significant effect on any CQA. Although a smaller amount of granulating fluid resulted in more favorable CQA outcomes, it also caused a decrease in flowability due to the generation of fine particles. This could pose a problem when scaling up to production from the lab, thus requiring further research before transitioning to manufacturing. In this study, the optimization of the dissolution-enhanced gemifloxacin formulation is expected to contribute to the development of high-quality pharmaceutical products through a systematic formulation design approach. The dissolution similarity ($f_2 \geq 50$) achieved with the reference product Factive® at pH 4.5 further supports the potential for consistent in vivo performance of the optimized formulation, consistent with the solubility and bioavailability improvements reported in our companion study currently in press [17].

Conflicts of interest

The authors declare that no conflicts of interest exist.

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