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Optimization of immediate-release cilostazol tablets using Quality by Design (QbD) approach

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ABSTRACT

Cilostazol, recognized for its antiplatelet and vasodilatory properties, serves as a mainstay therapeutic agent in clinical management, targeting the alleviation of intermittent claudication associated with peripheral arterial disease. Despite its clinical efficacy, the pharmacological utility of cilostazol is delayed by its suboptimal absorption kinetics within the gastrointestinal tract. Given this limitation, the present study aimed to develop an optimized formulation of immediate-release (IR) cilostazol tablets employing the principles of Quality by Design (QbD). The general objective was to enhance the gastrointestinal absorption profile of cilostazol using combined disintegrants. The study investigated several parameters to develop an optimized formulation. The evaluation encompassed the micromeritic properties of the powder, quality control evaluations of tablet characteristics, and the identification of critical quality attributes (CQAs). Among the four trial formulations investigated, the third formulation, characterized by a low and high concentration ratio of microcrystalline cellulose (MCC) and crospovidone, emerged as the most promising. Notably, this formulation exhibited favorable results across all evaluated parameters, particularly demonstrating significant improvements in disintegration time. The observed enhancement in cilostazol's solubility suggests a synergistic effect provided by the addition of both MCC and crospovidone as disintegrants in the formulation.

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INTRODUCTION

Cilostazol, a 2-oxy quinolone derivative, has emerged as an essential therapeutic agent for the management of intermittent claudication, a debilitating symptom of peripheral arterial disease (PAD) characterized by narrowed or blocked arteries in the legs (Conte et al. 2018). By inhibiting the phosphodiesterase III enzyme, cilostazol increases cyclic adenosine monophosphate (cAMP) levels, leading to vasodilation and alleviation of PAD symptoms (Sahinturk 2023). Originally introduced to the market by Otsuka Pharmaceutical under the brand name Pletal, cilostazol enhances walking distance in individuals with peripheral vascular disease. The recommended dosage regimen typically consists of 100 mg taken twice daily, with 50 mg tablets available to accommodate different therapeutic needs.

However, cilostazol's therapeutic efficacy is prevented by its poor aqueous solubility, classifying it as a Class II drug under the Biopharmaceutics Classification System (BCS). This poor solubility, coupled with high permeability, poses significant formulation challenges, leading to low dissolution rates and

KEYWORDS

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absorption in the gastrointestinal (GI) tract. Enhancing cilostazol's solubility and dissolution rate is crucial for ensuring consistent therapeutic outcomes.

Various formulation strategies, including complexation, microemulsion, micelle formation, and polymeric micelle preparation, have been proposed to address the solubility challenges associated with poorly soluble drugs. Among these strategies, super disintegrants such as cross-linked polyvinylpyrrolidone (crospovidone) have demonstrated significant potential in enhancing tablet disintegration and dissolution rates, thereby playing a crucial role in improving drug bioavailability. (Bhalani 2022).

Crospovidone, an example of a cross-linked PVP polymer, belongs to the category of super disintegrants known for their remarkable ability to rapidly disintegrate tablets. Upon ingestion, super disintegrants like crospovidone rapidly absorb water, leading to swelling and the generation of mechanical forces that distort the tablet matrix, facilitating rapid tablet disintegration (Pather 2024). This mechanism emphasizes the importance of super disintegrants in enhancing the dissolution properties of poorly soluble drugs like cilostazol, ultimately contributing to improved drug bioavailability.

Microcrystalline cellulose (MCC), a white, odorless, and insoluble cellulose derivative, has gained importance in pharmaceutical formulations due to its unique physicochemical properties. With advantages including high crystallinity, small particle size, and superior liquidity, MCC serves as an ideal filler, diluent, and disintegrant in tablet formulations, facilitating the rapid disintegration and dissolution of tablets in the GI tract (Hao 2024).

Quality by Design (QbD) is a principle characterized by clear objectives, product and process understanding, and quality risk management. Its implementation aims to prevent variations and defects in the final product, thereby enhancing product development, manufacturing efficiencies, and post-approval change management (Yu et al. 2014). Dr. Joseph Juran, the pioneer of QbD, emphasized that product design supports most quality issues, advocating for the integration of quality into the product design process. QbD entails delineating the intended product attributes or critical quality attributes (CQAs), correcting factors that impact CQAs on critical material attributes (CMAs) or raw materials, all of which are governed by critical process parameters (CPPs). In the context of IR cilostazol tablets, its efficacy depends on the rapid dissolution and absorption of the active ingredient. Disintegration and dissolution rates stand as important CQA for IR tablets, directly influencing product quality and absorption. Excipients, including disintegrants, exert significant influence on the disintegration and dissolution mechanisms of dosage forms.

The objective of this study was to develop an optimized formulation of IR tablets, facilitating the rapid absorption of cilostazol in the gastrointestinal tract. This endeavor encompassed determining the optimal disintegrant ratio of MCC and crospovidone and establishing a formulation guided by the QbD approach, customized to produce IR cilostazol tablets of desirable quality aligned with predetermined CQAs.

MATERIALS AND METHODS

Materials

The cilostazol was purchased from Xi'an Henrikang Biotech Co., Ltd.; microcrystalline cellulose (MCC) and polyvinylpyrrolidone K30 (PVP K30) from Pharmatechnica Laboratory Inc.; crospovidone from Compact Pharmaceutical; magnesium stearate (MgSt) from Aishite Trading Corp.; and isopropyl alcohol (IPA), sodium lauryl sulfate (SLS), and corn starch from Belman Laboratories. All solvents used were analytical grade.

Formulation and optimization of IR cilostazol tablets

To investigate the impact of combined disintegrants on critical quality attributes (CQAs) of IR cilostazol tablets, a 2^2 factorial design was employed. Quality by design (QbD) principles were implemented using Design Expert software to conduct the experimental design. The factorial design comprised 4 experimental trials, with each trial involving the production of 3 batches per run, wherein two independent variables were manipulated at two levels each. The first variable pertained to the quantity of microcrystalline cellulose (MCC) at high (19.5 mg) and low (6.5 mg) levels, and crospovidone at high (10 mg) and low (4 mg) levels. The second variable was the number of disintegrants (MCC and crospovidone). The outcome variables of interest encompassed the assessment of predetermined CQAs or responses, including friability, tensile strength, disintegration time, assay content, and dissolution rate.

Formulation of cilostazol IR tablets

Cilostazol immediate-release (IR) tablets were formulated according to the composition indicated in Table 1. A comprehensive assessment of drug-excipient compatibility revealed no evidence of chemical or physical instability when cilostazol was combined with the excipients employed in the formulation. Fourier-transform infrared spectroscopy (FTIR) and differential scanning calorimetry (DSC) analyses further confirmed the compatibility findings. These results substantiated the good selection of excipients for the formulation of IR tablets (Diño et al. 2023).

The formulation strategy was predicated on preliminary trial formulations, which indicated that a blend of microcrystalline cellulose (MCC) and crospovidone as dual disintegrants, varied in amounts, yielded optimal results in terms of flowability, compressibility, and disintegration rate. The weights of MCC (X1) and crospovidone (X2) were designated as the formulation variables for the optimization of the IR cilostazol tablets due to their perceived significant impact on tablet quality. Additionally, other excipients utilized included magnesium stearate (MgSt), isopropyl alcohol (IPA), sodium lauryl sulfate (SLS), polyvinylpyrrolidone K30 (PVP K30), and corn starch.

All raw materials underwent pre-sieving using a 40-micrometer sieve, except for crospovidone and magnesium stearate. Subsequently, cilostazol, MCC, SLS, PVP K30, and corn starch were blended in a sieve pan using a spatula. Isopropyl alcohol was introduced to form a wet mass, followed by de-lumping of the powder blends using a 30-micrometer sieve and subsequent oven drying (DSA-500D) at 40°C until moisture content ranged between 2 and 5%. Crospovidone and magnesium stearate were then integrated into the final blend, which underwent sieving once more using a 30-micrometer sieve before compression into tablets using the TM-1 Single Punch Tableting Machine (Scigate Technology Corp.).

Table 1: Composition IR cilostazol tablets

Raw material	Amount per dosage unit (mg)			
	F1	F2	F3	F4
Cilostazol	50	50	50	50
Microcrystalline cellulose (MCC)	6.5	19.5	6.5	19.5
Crospovidone	4	4	10	10
Magnesium stearate (MgSt)	1	1	1	1

Isopropyl alcohol (IPA)	q.s.	q.s.	q.s.	q.s.
Sodium lauryl sulfate (SLS)	2	2	2	2
Polyvinylpyrrolidone K30 (PVP K30)	3	3	3	3
Corn starch	63.5	50.5	57.5	44.5

Evaluation of powder blends

The micromeritics evaluation of the powder blend encompassed several parameters, including moisture content, bulk density, angle of repose, tapped density, Hausner's ratio, and Carr's compressibility index, which were assessed using standard procedures. Moisture content analysis was conducted utilizing a moisture analyzer (Shimadzu MOC63).

Evaluation of IR cilostazol tablets

The assessment of quality control parameters for the immediate release (IR) cilostazol tablets comprised an evaluation, including organoleptic characteristics, thickness, diameter, and weight variation. These evaluations were conducted utilizing established and standardized procedures to ensure the accuracy and reliability of the results.

Evaluation of the Critical Quality Attributes (CQAs)

Friability
The assessment of friability for the IR cilostazol tablets was performed utilizing a friabilator (Copley FRV 200) following standard procedures. Initially, twenty (20) tablets underwent weighing before being subjected to rotational forces within the friabilator, operating at a rotational speed of 25 revolutions per minute (rpm) for 4 minutes. After 100 rotations, the tablets were reweighed after dedusting procedures. The determination of friability was achieved by calculating the percentage of weight loss incurred by the tablets during the testing process. This calculation was conducted by comparing the initial and final weights of the tablets, considering any weight reduction attributable to mechanical abrasion or fragmentation occurring during rotational movement. The requirement for the percent friability should be NMT 0.8% loss for new formulations.

Tensile strength
The tensile strength of the IR cilostazol tablets was calculated using its hardness, diameter, and thickness. It was calculated as follows:

$$\% \text{ friability} = \frac{\textit{initial weight of the tablets} - \textit{final weight of the tablets}}{\textit{initial weight of the tablets}} \times 100$$

Disintegration
The disintegration test (DT) of IR cilostazol tablets was conducted employing a DT apparatus (Labtron LDIT A12) using standardized procedures. Each tablet was individually placed within one of six tubes situated in the basket-rack assembly, accompanied by a disintegration disk. The distilled water served as the immersion medium, maintained at a controlled temperature of 37 ± 2 °C throughout the test. The disintegration process was observed for a predetermined period of 5 minutes. Upon completion of the 5 minutes, the basket-rack assembly was withdrawn from the distilled water, and the time required for complete disintegration of the tablets was recorded.

Assay
The content of the active pharmaceutical ingredient in the IR cilostazol tablets was assayed using high-performance liquid chromatography (HPLC, PerkinElmer Flexar). The mobile phase used was 25:75 ratio of acetonitrile (ACN) and methanol. The sample solution was prepared by diluting 26 mg of cilostazol powder blend into 10 mL of methanol. The solution was then filtered using a nylon filter of 0.45 mcm pore size. A 25 µL sample solution was injected into the HPLC. The chromatograms were then observed, and the areas of the prominent peaks were noted. The labeled amount of cilostazol should be within 90-110%, which was calculated using the following formula:

$$\% \text{ cilostazol} = (R_U / R_S) \times (C_S / C_U) \times 100$$

Where,
- R_U = peak response of cilostazol from the sample solution
- R_S = peak response of cilostazol from the secondary standard solution
- C_S = concentration of cilostazol in the secondary standard solution (mg/mL)
- C_U = nominal concentration of cilostazol in the sample solution (mg/mL)

Dissolution
The dissolution test was conducted utilizing USP Dissolution paddle apparatus type 2 operating at a rotational speed of 75 revolutions per minute (rpm) for 60 minutes. The dissolution medium comprised 900 mL of a solution containing 0.30% sodium lauryl sulfate (SLS) dissolved in water. To prepare the sample solution, not less than 20 mL of the standard solution was subjected to filtration through a nylon filter possessing a pore size of 0.45 µ.

The amount of the dissolved cilostazol content in the sample was performed utilizing a UV-VIS spectrophotometer set to a wavelength of 257 nanometers (nm), with the dissolution medium serving as the blank reference. The labeled amount of cilostazol dissolved must be not less than 80% (Q). To calculate this, the following formula was used:

$$\% \text{ dissolved} = (AU/AS) \times CS \times V \times D \times (1 / L) \times 100$$

Where,
- AU = absorbance of the sample solution
- AS = absorbance of the standard solution
- CS = concentration of USP cilostazol RS in the standard solution (mg / mL)
- V = volume of the medium, 900 mL
- D = dilution factor for the sample solution
- L = label claim (mg / tablet)

RESULTS

Evaluation of the powder blends

Table 2 shows the results of the powder blend characteristics of the 4 formulations. The results were compared to the USP specifications and were found to be within acceptable limits. Specifically, the test results of all the formulations from the angle of repose, CCI, and Hausner's ratio indicated excellent flowability. As for the moisture content, all powders possessed a moisture content of less than 5%. Hence, the powder blend for all formulations can be compressed through direct compression.

Table 2: Results of powder blend evaluation

Test	Specification	F1	F2	F3	F4
Moisture content	Not more than 5%	4.67 ± 0.24	4.28 ± 0.47	4.07 ± 0.69	4.65 ± 0.08
Angle of repose	Excellent: ≤ 30°	22.03 ± 2.48	20.31 ± 0.34	19.73 ± 1.23	21.50 ± 1.03
Bulk density		0.43 ± 0.04	0.45 ± 0.02	0.49 ± 0.04	0.46 ± 0.02
Tapped density		0.46 ± 0.04	0.47 ± 0.02	0.51 ± 0.04	0.50 ± 0.01
Carr's compressibility index	Excellent: <10%	6.15 ± 2.16	4.03 ± 1.56	1.02 ± 0.01	2.23 ± 1.17
Hausner's ratio	Excellent: 1.00 - 1.11	1.07 ± 0.02	1.04 ± 0.02	1.03 ± 0.02	1.02 ± 0.01

Evaluation of the IR cilostazol tablets

Quality control parameter evaluation: Organoleptic characteristics, thickness, diameter, hardness, and weight variation of the IR cilostazol tablets

The organoleptic evaluation of IR cilostazol tablets involved a visual examination to assess their physical characteristics. Examination showed the absence of excessive powders, swelling, mottling, discoloration, and alterations in appearance. However, a portion of the produced IR cilostazol tablets from Formulations 1 to 4 exhibited chipping and cracking, indicative of surface defects.

For the results of the organoleptic assessment and other quality parameters of the four formulations, Formulations 1 and 2 showed white, round tablets with shiny surfaces, while exhibiting some occurrence of chipping and cracking. Minor changes in tablet color were observed for Formulations 3 and 4, which appeared dull white with similar surface characteristics. This minor color change was attributed to the duration of heating of the powder blends to achieve the allowable moisture content.

The analysis of thickness, diameter, tensile strength, and weight variation was conducted for the four formulations, with results summarized in Table 3. Tablet thickness ranged from 3.27 mm to 3.34 mm, while diameter varied between 7.03 mm and 7.06 mm.

The weight variation assessment demonstrated that Formulations 1 to 4 were within an acceptable range specified as ±7.5% deviation from the target weight of 130 mg. Results indicated weights ranging from 127.32 mg to 133.49 mg, meeting the desired weight specifications as shown in Table 3.

Table 3: Quality control parameters for IR cilostazol tablets

Formulation	Composition (in mg)		CQAs (Responses)*				
	MCC	Crospovidone	Friability (% loss)	Tensile strength (kPa)	Disintegration (secs)	Assay (% cilostazol)	Dissolution (%)
1	6.5	4	1.49 ± 1.04	325.68 ± 32.41	253.44 ± 2.87	102.57 ± 2.64	83.76 ± 0.93
2	19.5	4	0.79 ± 0.07	371.13 ± 7.20	273.78 ± 16.32	107.73 ± 0.74	85.72 ± 2.38
3	6.5	10	0.61 ± 0.12	465.80 ± 74.56	209.67 ± 37.26	105.21 ± 5.33	84.79 ± 2.66
4	19.5	10	0.64 ± 0.04	570.81 ± 23.99	224.33 ± 8.84	108.93 ± 1.96	82.31 ± 1.75

**Mean ± standard deviation (n=3)*

Evaluation of the Critical Quality Attributes (CQAs)

Table 4 shows the result of the evaluation of the CQAs of the formulations. The friability of the formulations ranged from 0.61 to 1.49 % loss, with Formulations 2 to 4 within the USP specifications. For tensile strength, Formulation 1 had the lowest tensile strength (325.68 ± 32.41 kPa) while Formulation 4 had the highest (570.81 ± 23.99). The disintegration time for F1, F2, F3, and F4 ranged from 209.67 sec. to 273.78 sec, which were all within the requirements of NMT 5 min. The result of the assay indicated that Formulations 1 to 4 passed the USP specifications of 90 – 110% content of cilostazol in the IR tablets which is necessary to achieve the desired therapeutic effect. The IR cilostazol tablets were also subjected to USP dissolution apparatus 2. All formulations were within the specifications of NLT 80% dissolved cilostazol.

Optimization of IR cilostazol tablets containing two disintegrants: MCC and crospovidone

The optimization of IR cilostazol tablets was determined based on the analyzed CQAs using ANOVA in Design-Expert version 13 (Stat-Ease, Inc. Minneapolis). Table 4 shows the analysis of the ANOVA model for the prediction of friability, tensile strength, disintegration, assay, and dissolution. The Model F-value indicates whether the model terms are significant. In this case, the two disintegrants were not significant model terms for friability, tensile strength, assay, and dissolution. However, the Model F-value of 9.55 (p-value = 0.0060) implied that the model was significant. In this case, crospovidone was a significant model term (F=16.73; p-value=0.0027).

Adequate Precision measures the signal-to-noise ratio. A ratio greater than 4 is desirable. A ratio of less than 4 for friability, tensile strength, assay, and dissolution indicates inadequate

signal. In contrast, a ratio of 6.4969 for disintegration indicates adequate signal, hence, the model can be used to navigate the design space.

Table 4: Summary of ANOVA model for the different response factors

Response factor	ANOVA		Fit statistics			Lack of fit	
	F-value	Prob>F	R^2	Adeq. Prec	C.V %	F-value	Prob.>F
Friability	1.84	0.2182	0.4082	2.8999	59.62	1.4700	0.2602
Tensile strength	1.10	0.3735	0.1965	2.1014	27.60	0.0174	0.8982
Disintegration	9.55	0.0060	0.6796	6.4969	8.21	0.0553	0.8199
Assay	2.40	0.1428	0.4742	3.4940	2.97	-	-
Dissolution	1.54	0.2765	0.3668	2.8979	2.42	-	-

Final equation for the prediction of disintegration time

Disintegration time = 277.185 + 1.34615 * MCC + -7.76852 * Crospovidone

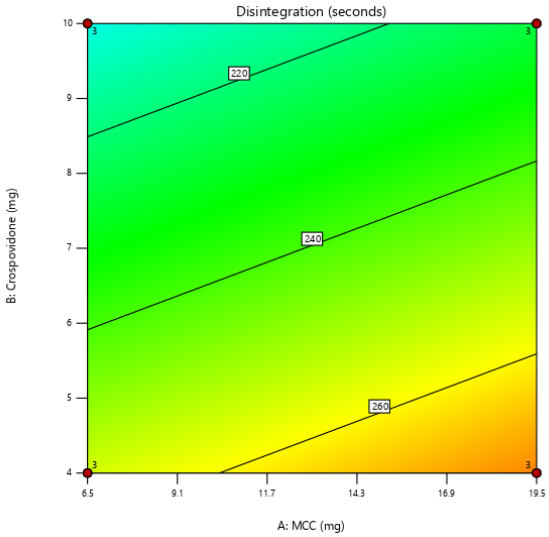

Figure 1: Contour plot showing the effect of MCC and crospovidone on disintegration time

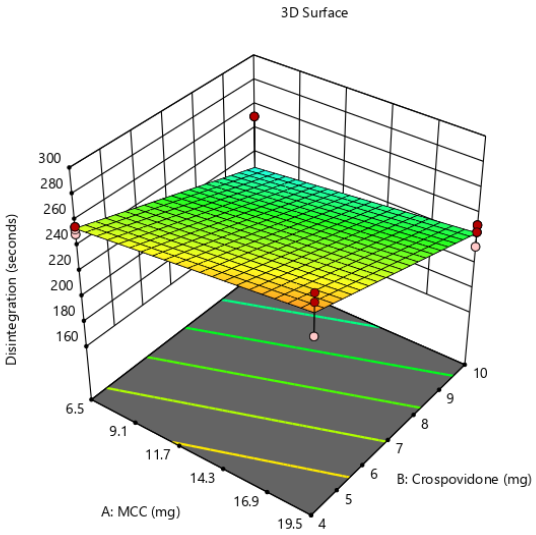

Figure 2: Response surface plot (3D) showing the effect of MCC and crospovidone on disintegration time

The model obtained for the disintegration time was found to be significant with F-value and p-value of 9.55 and 0.0060, respectively. Furthermore, it was found that the disintegration time was shorter with the increase in the concentration of crospovidone and the decrease in the concentration of MCC. A confirmatory test was able to verify these results.

DISCUSSION

The assessment of the powder blends indicates that the formulations possess attributes conducive to flowability and compressibility as specified by the United States Pharmacopeial Convention guidelines (2020). Notably, among the formulations tested, Formulation 3 exhibited superior characteristics, characterized by a low amount of microcrystalline cellulose (MCC) and a high amount of crospovidone. After compression into tablets, standard procedures were employed to evaluate quality parameters including organoleptic properties, thickness, diameter, tensile strength, and weight variation of the IR cilostazol tablets.

The observed color variations in Formulations 1 and 2 were attributed to the duration of heating the powder blends to achieve the allowable moisture content of not more than 5%. A glossy tablet surface was achieved across all formulations, while instances of surface defects such as chipping were noted in some tablets across all formulations. Variability in thickness, particularly noted in Formulations 1 and 2, may be attributed to inconsistencies in the compression machinery. However, overall results indicated compliance with United States Pharmacopeia (USP) standards for thickness, diameter, and weight variation among Formulations 1 to 4.

Upon subjecting the tablets to friability testing, only Formulation 1 exhibited a percentage loss of 1.49%, failing to meet specifications. This result suggests that Formulation 1, containing low amounts of both MCC and crospovidone, was susceptible to particle loss under mechanical stress or abrasion, as encountered during coating, storage, transportation, and handling (Zhao 2022). Formulations 2 to 4, exhibiting losses within acceptable limits, maintained either low or high amounts of crospovidone. Formulations 3 and 4, with satisfactory results, incorporated a high amount of crospovidone, specifically 10 mg.

Tensile strength, a critical attribute of tablets, is the ability of tablets to withstand the rigors of packaging, transportation, and tablet coating processes. It is related to compression force, which in turn influences tablet hardness (Juban 2015). Parameters such as tablet hardness, diameter, and thickness are integral in calculating tensile strength. The specification for the hardness of IR cilostazol tablets, suitable for commercial production and subsequent distribution, ranges from 3 to 7 kg/cm2, equivalent to 294.20-686.47 kPa (Pitt and Heasley 2013). Formulations 1 to 4, as shown in Table 4, met this specification as well as the US Pharmacopeia (USP) standard, which requires a minimum of 12 kPa. However, Formulations 1, 3, and 4 exhibited high standard deviations, which was attributed to compression machine issues. Variations in the tensile strength among the different formulations may also be due to varying amounts of moisture present in the powder blend. Moisture content at an acceptable level acts as a binder which increases the tablet's hardness (Saleem et al. 2014).

The disintegration rate, recorded in seconds, is the time taken for complete disintegration of IR cilostazol tablets, leaving no residue on the test apparatus screen or adhering to the lower surface of the disk. All 4 formulations disintegrated within 5 minutes, meeting specifications. The disintegration rate for formulations containing varying amounts of MCC and crospovidone correlated with enhanced solubility of cilostazol, particularly Formulation 3, which exhibited the fastest disintegration rate among the four formulations.

The result of the assay demonstrated compliance with the USP specifications. However, there were notable variations in the result. The high variations in the % cilostazol may indicate insufficient or non-uniform blending of the powders before compression.

Dissolution rate results for Formulations 1 to 4 indicated compliance with the USP requirement of not less than 80% dissolution rate. Dissolution rate directly impacts drug absorption, emphasizing the effectiveness of the IR cilostazol tablets in releasing the active pharmaceutical for absorption into the bloodstream (Siew 2016). Hence, the IR cilostazol tablets produced from each formulation would be bioavailable.

With the QbD approach, the batches of the four formulations with different concentrations of MCC and crospovidone had the desired flowability and compressibility characteristics. In addition, each formulation passed the specifications for quality tablet characteristics. Given the distinctive findings of each formulation, Formulation 3, with a low-high concentration of MCC and crospovidone, showed the best results among the 4 formulations. Accordingly, the concentrations of MCC and crospovidone in the formulation had significantly contributed to achieving the desired results for the determined CQAs for the IR cilostazol tablets.

In the pilot scale of optimized formulation, all three batches were within the specifications in the tests conducted for the evaluation of powder blend and tablet characteristics.

CONCLUSION

In conclusion, the use of two disintegrants (MCC and crospovidone) showed an improvement in the solubility of cilostazol. Among the four formulations tested, a low-high concentration of MCC and crospovidone (Formulation 3) yielded the most desirable results in all the CQAs, especially the disintegration time. The findings require further studies including in-vivo tests to fully evaluate the efficacy and toxicity of the drug.

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CONFLICT OF INTEREST

The authors declare that they have no known competing financial interests or personal relationships that could inappropriately influence the work reported in this paper.

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