

DEVELOPMENT OF DISCRIMINATING AND IN VIVO CORRELATING DISSOLUTION METHOD FOR BCS CLASS II CILOSTAZOL IMMEDIATE RELEASE TABLET FORMULATION

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ABSTRACT

Cilostazol is used to treat symptoms of intermittent claudication in peripheral vascular disease. It is classified as a Class II drug in the Biopharmaceutics Classification System, exhibiting low solubility and poor bioavailability, which makes pharmacokinetic evaluation essential during product development. This study aimed to develop a discriminative dissolution medium and method reliable for predicting the in vivo results of Cilostazol tablets. In this study, dissolution methods were developed according to regulatory guidelines using water (per USP monograph) and buffer solutions (pH 1.2, 4.5, and 6.8) supplemented with 0.05–0.30% sodium lauryl sulfate (SLS). Testing was performed on a formulated sample and a comparator product (n=12 each) at 37 ± 0.5 °C, with varying paddle speeds (50–75 rpm) and volumes (500–900 mL). The most biorelevant and discriminating condition—a pH 1.2 buffer with 0.05% SLS, 50 rpm paddle speed, and 500 mL volume—was identified as the most suitable in vitro profile for distinguishing the test formulation from the comparator and for predicting in vivo results.

Keywords: Cilostazol, Biopharmaceutics Classification System, Biorelevant medium, discriminating dissolution method, Bioavailability

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PENGEMBANGAN METODE DISOLUSI YANG DISKRIMINATIF DAN BERKORELASI SECARA IN VIVO UNTUK FORMULASI TABLET LEPAS CEPAT (IMMEDIATE RELEASE) CILOSTAZOL KELAS BCS II

ABSTRAK

Cilostazol digunakan untuk menangani gejala klaudikasi intermiten pada penyakit vaskular perifer. Obat ini diklasifikasikan sebagai obat Kelas II dalam Biopharmaceutics Classification System, yang menunjukkan kelarutan rendah dan bioavailabilitas buruk, sehingga evaluasi farmakokinetika menjadi sangat penting selama pengembangan produk. Penelitian ini bertujuan untuk mengembangkan media dan metode disolusi diskriminatif yang andal untuk memprediksi hasil in vivo dari tablet Cilostazol. Dalam studi ini, metode disolusi dikembangkan sesuai dengan pedoman regulasi menggunakan air (berdasarkan monografi USP) dan larutan dapar (pH 1,2; 4,5; dan 6,8) yang ditambahkan natrium lauril sulfat (SLS) 0,05–0,30%. Pengujian dilakukan terhadap sampel formulasi dan produk pembandingan (masing-masing n=12) pada suhu 37 ± 0,5 °C, dengan variasi kecepatan pedal (50–75 rpm) dan volume (500–900 mL). Kondisi yang paling biorelevan dan diskriminatif—dapar pH 1,2 dengan SLS 0,05%, kecepatan pedal 50 rpm, dan volume 500 mL—diidentifikasi sebagai profil in vitro yang paling sesuai untuk membedakan formulasi uji dari pembandingan serta untuk memprediksi hasil in vivo.

Kata Kunci: Cilostazol, Sistem Klasifikasi Biofarmasetika, Medium Biorelevan, Metode Disolusi diskriminatif, Ketersediaan Hayati

INTRODUCTION

Cilostazol is a drug to treat vascular claudication symptoms, indicated by muscle pain or cramping due to insufficient blood flow. The drug works by inhibiting the aggregation of platelets and vasodilation. By preventing platelet clumping, Cilostazol reduces the risk of vascular obstruction, while its vasodilatory action enhances blood flow (Kherallah et al. 2022; Schrör 2002). This action improves blood circulation and increases circulation to body cells. Cilostazol is classified in the Biopharmaceutics Classification System (BCS) as a Class II drug, characterized by poor solubility and high permeability. This classification is based on its physicochemical properties specifically low aqueous solubility (6 µg/mL at 25°C) (Bibi et al. 2022) and high permeability as demonstrated by the apparent permeability coefficient of 1.92×10^{-5} cm/s across a Caco-2 cell monolayer which is above acceptable high-permeability threshold value ($P_{app} > 1 \times 10^{-6}$ cm/s) (Toyobuku et al. 2003).

Since Cilostazol is classified as a BCS Class II drug, it is important to evaluate its pharmacokinetics, especially during drug product development. Dissolution testing is a widely used in-vitro technique for assessing drug release and predicting in vivo pharmacokinetic results of a drug formulation. Furthermore, in vitro dissolution testing is a critical requirement established by regulatory authorities such as the U.S. Food and Drug Administration (FDA) to ensure the safety, efficacy, and quality of oral drug products. For Cilostazol tablets, the FDA dissolution database does not specify a standard dissolution method. However, the official monograph in the United States Pharmacopeia (USP) for Cilostazol tablets recommends using water containing sodium lauryl sulfate (USP 2025a). According to FDA guidance (FDA, 1997), the development of an in vitro dissolution medium should employ an aqueous system within a pH range of 1.2 to 6.8, with the buffer ionic strength aligned with the USP. Due to the absence of an FDA-recommended dissolution medium for Cilostazol, and considering its low aqueous solubility, an appropriate medium and method must be carefully developed to ensure a reliable in vitro method to predict in vivo results.

Previous studies on Cilostazol focused on advance formulation approaches and modelling for bioavailability enhancement and in vitro/in vivo correlation (IVIVC) development. For reference literature (Jinno et al. 2008), which discusses wet milling of Cilostazol to sub-micron particle size followed by co-precipitation with sugar alcohol, and subsequent compression, which was further evaluated for the improvement of oral bioavailability on male beagle dogs and its IVIVC using USP apparatus IV. The other literature (Min et al. 2024) discussed IVIVC of two extended-release formulations of Cilostazol, while another article (Kamada et al. 2009) discussed IVIVC of Cilostazol based on the GITA (GI-Transit-absorption) model; however dissolution method was not mentioned. In contrast, our study focuses on the development of a dissolution method for conventionally wet-granulated Cilostazol tablets, aiming to establish IVIVC with a comparator product using USP apparatus II. To the best of our knowledge, this approach has not yet been reported. In this study, we tried to develop a discriminative dissolution medium and method that is reliable to predict in vivo results for our formulation, Cilostazol tablet.

MATERIALS AND METHODS

Materials

Cilostazol drug substance obtained from Glenmark Pharmaceuticals (Mumbai, India), Cilostazol working standard has been derivatized from the drug substance using the Cilostazol reference standard from USP (Maryland, USA). Pletaal tablet (Otsuka, Indonesia) containing 50 mg of Cilostazol acquired from commercial sources within their shelf-life period. Methanol (HPLC grade), Sodium lauryl sulphate (for analysis grade), Sodium chloride (for analysis grade), Hydrochloric acid 37% (for analysis grade), Sodium hydroxide pellets (for analysis grade) were purchased from Merck (Darmstadt, Germany). Water used was purified using Milli-Q Advantage A10 water purification system (Millipore, Bedford, USA). The 0.45 µm cellulose membrane filter used was from MDI technology (Pennsylvania, USA). The excipient used in formulation consists of microcrystalline cellulose (Mingtai Chemical, Taiwan), corn starch (Roquette, Italy), Hypromellose (Shin-Etsu

Chemical, Japan), Carboxymethylcellulose calcium (Nichirin Chemical, Japan), and magnesium stearate (Faci Asia, Singapore).

Apparatus

Dissolution testing was performed using a Pharmatest PTWS 1210 dissolution tester equipped with 12 vessels (Pharmatest, Hainburg, Germany), configured as USP Apparatus II (paddle method). Sample analysis was performed using a double-beam UV-Visible spectrophotometer (Shimadzu UV-1800, Kyoto, Japan) integrated with UV Probe software for data acquisition.

Formulation preparation

Cilostazol tablets were prepared using a wet granulation method. The drug substance was mixed with microcrystalline cellulose and corn starch using a high-shear mixer. A binder solution containing Hypromellose dissolved in purified water was added gradually under controlled mixing conditions. The wet mass was granulated and then dried at 70 °C until the moisture content reached about 2–3%. The dried granules were milled using a Quadro Comil and blended with extragranular excipients, including carboxymethylcellulose calcium and magnesium stearate. The final blend was compressed into tablets using a rotary tablet press with controlled fill depth and compression force.

Preparation of Reference Solution

Reference solution for dissolution with 900 mL medium volume

Cilostazol working standard equivalent to 55.5 mg was dissolved in a 50 mL volumetric flask. 40 mL of methanol was added. The solution was sonicated for approximately 5 minutes to dissolve and was made to volume with methanol. The solution was diluted to achieve a concentration of 11.1 µg/mL with the dissolution medium. Absorbance was measured at 257 nm.

Reference solution for dissolution with 500 mL medium volume

Cilostazol working standard equivalent to 50.0 mg was dissolved in a 50 mL volumetric flask. 40 mL of methanol was added. The solution was sonicated for approximately 5 minutes to dissolve and made to volume with methanol. The solution was diluted

to get a 20 µg/mL concentration with dissolution medium. Absorbance was measured at 257 nm.

Dissolution testing procedures

The dissolution medium was prepared according to USP guidelines (USP 2025b), using water and buffer solutions (Hydrochloric acid buffer pH 1.2, acetate buffer 4.5, and phosphate buffer 6.8) supplemented with various concentrations of sodium lauryl sulfate (SLS) ranging from 0.05% to 0.30%, added per liter of medium as required. Twelve units of test samples and a comparator were tested in each dissolution medium. The methods were also evaluated by varying paddle speeds from 75 to 50 rpm and dissolution volume from 900 to 500 mL. The dissolution temperature was maintained at 37 ± 0.5 °C, and the dissolution vessels were covered to minimize evaporation. At each sample time interval (5, 10, 15, 30, 45, and 60 min), an exact volume of the sample (10 mL) was withdrawn from each vessel and immediately replenished with an identical volume of medium to maintain a dissolution sink condition. The 4.0 mL aliquot in each sampling point was taken into a 20 mL volumetric flask and diluted to volume with dissolution media. The samples were filtered using a 0.45 µm cellulose membrane filter. The amount of Cilostazol in samples was measured using a UV-Visible spectrophotometer, and the absorbance value was converted into a percentage of drug release, with a correction factor at each sampling point. A graph was plotted against time vs. percentage of drug release to give dissolution profiles. Further statistical analysis of percentage drug release over time between the formulated sample (Formula-1/Formula-2) and the comparator product was conducted to evaluate the equivalence profile by using the similarity factor (f_2).

Bioavailability Study

Healthy male and female adults participated as subjects. The study was conducted in a randomized, open-label, two-period, two-sequence crossover study under fasting conditions. The participating subjects were required to have an overnight fast, and on the next morning (the first day of each period), were given orally one tablet of the test drug (Formula-1 or Formula-2) or one tablet of the comparator product (Pletaal Tablet 50

mg, ex. PT Otsuka Indonesia). Blood samples were drawn immediately before taking the drug (control) and at 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 12, 16, 24, 36, and 48 hours. The study protocol was approved by the Ethics Committee of the Faculty of Medicine, University of Indonesia (Approval No.: KET-702/UN2.F1/ETIK/PPM . 00.02/2019).

RESULTS AND DISCUSSION

Initial dissolution study

According to the official monograph in the USP, the recommended dissolution medium for Cilostazol tablets is water containing 0.3% sodium lauryl sulfate (SLS), using USP Apparatus II (paddle) at 75 rpm with a dissolution volume of 900 mL (USP, 2025a). The incorporation of SLS is necessary due to the poor aqueous solubility of Cilostazol. In line with FDA guidance, in vitro dissolution media should be aqueous-based, with a pH range of 1.2 to 6.8, and buffer ionic strength consistent with USP standards. However, no specific FDA-

recommended dissolution method exists for Cilostazol. Given its low solubility, careful development of an appropriate dissolution medium and method is essential to ensure reliable in vitro results that correlate with in vivo outcomes. Therefore, as an initial step in this study, we developed a dissolution method to evaluate our Cilostazol formulation based on both regulatory and pharmacopeial guidelines, as shown in Table 1.

Based on the proposed design, a comparative dissolution profile study was conducted. The results are summarized in Table 2, and the dissolution profiles are presented in Figure 1. The similarity factor (f_2) between the comparator product (Pletaal Tablet 50 mg) and the test formulation (Formula-1) indicated that Formula-1 exhibits a comparable dissolution profile to Pletaal tablet 50 mg, with a range of 56 - 72. Further analysis was then performed to evaluate the pharmacokinetic profile of the Formula-1 sample to confirm its in vivo performance.

Table 1. Design of dissolution testing method of Cilostazol tablets.

Medium	Apparatus	Volume	Rate	Sampling time (minutes)
Water + 0.3% SLS (QC medium release according to USP monograph)	Type II USP (Paddle)	900 mL	75 rpm	5, 10, 15, 30, 45, 60
pH 1.2 + 0.15% SLS	Type II USP (Paddle)	900 mL	75 rpm	5, 10, 15, 30, 45, 60
pH 4.5 + 0.15% SLS	Type II USP (Paddle)	900 mL	75 rpm	5, 10, 15, 30, 45, 60
pH 6.8 + 0.15% SLS	Type II USP (Paddle)	900 mL	75 rpm	5, 10, 15, 30, 45, 60

Table 2. Result of dissolution testing of Cilostazol tablets in several dissolution medium.

Time (minutes)	Water +0.3% SLS		pH 1.2 + 0.15% SLS		pH 4.5 + 0.15% SLS		pH 6.8 +0.15% SLS	
	Pletaal tablet 50 mg BN: TA 8946	Formula-1	Pletaal tablet 50 mg BN: TA 8946	Formula-1	Pletaal tablet 50 mg BN: TA 8946	Formula-1	Pletaal tablet 50 mg BN: TA 8946	Formula-1
5	31	36	33	30	31	29	36	29
10	61	52	49	59	51	53	60	56
15	75	64	58	66	59	61	69	66
30	86	79	71	74	69	74	83	76
45	92	88	78	78	72	77	87	78
60	94	93	84	81	77	82	92	82
f_2	56		60		72		60	

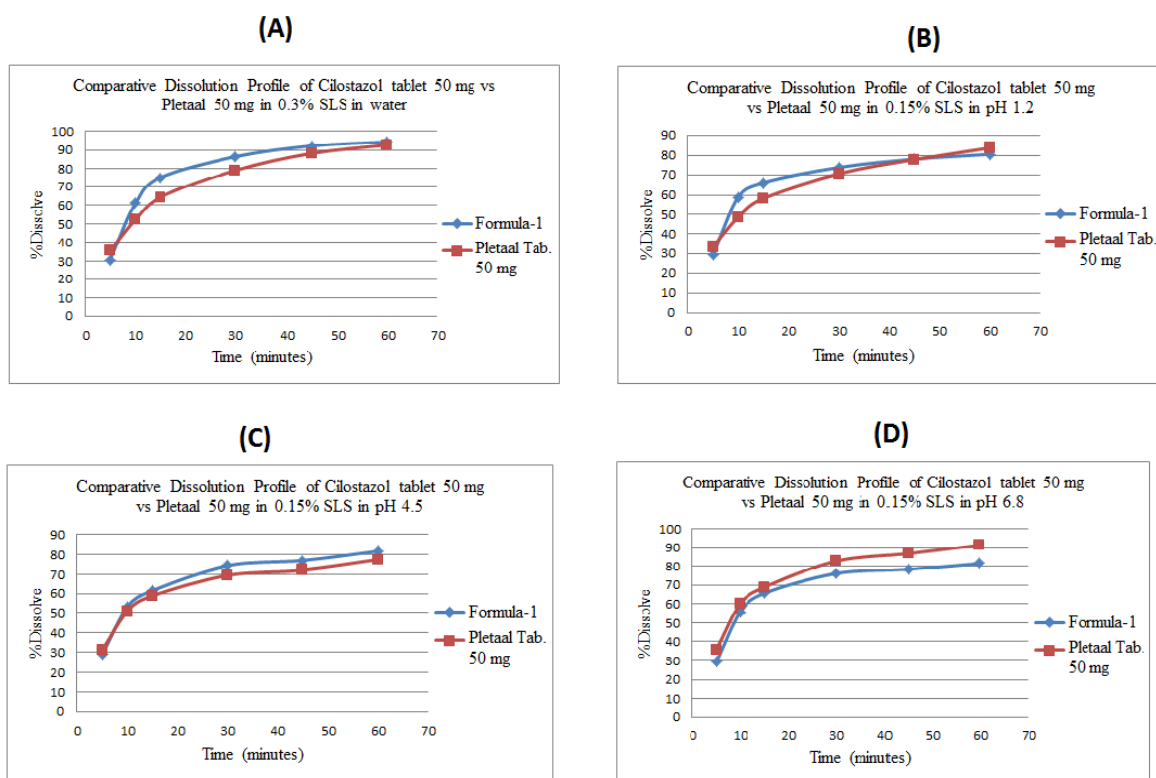


Figure 1. Comparative dissolution profiles of Formula-1 vs. Pletaal 50 mg in various media: (A) Water + 0.3% SLS (USP), (B) pH 1.2 + 0.15% SLS, (C) pH 4.5 + 0.15% SLS, and (D) pH 6.8 + 0.15% SLS.

Pharmacokinetics study of initial dissolution method

The Formula-1 test formulation was administered to human volunteers. The pharmacokinetic results are shown in Table 3 with corresponding profiles illustrated in Figure 2. The data demonstrated that the comparator product exhibits a lower pharmacokinetic profile compared to Formula-1, as indicated by the area under the curve (AUC) and maximum plasma concentration (C_{max}) values presented in Table 3. The statistical analysis with a 90% confidence interval for the C_{max} of the test

product was above the upper bioequivalence limit of 125% (Table 4), thus failing to meet criteria for bioequivalence, and it can be concluded that Formula-1 is not bioequivalent to the comparator product. Despite the similarity observed in the in-vitro dissolution profiles ($f_2 > 50$ under all tested conditions), the bioinequivalent result suggests the absence of in-vitro-in-vivo correlation for the initially designed dissolution method. Therefore, further optimization of the dissolution method is needed to develop a discriminative dissolution method that can accurately predict in vivo results.

Table 3. Pharmacokinetic parameters (AUC and C_{max}) of Cilostazol 50 mg (Formula-1) vs. Pletaal 50 mg (Otsuka)

Parameter	Test Drug (Formula-1)		Comparator Drug (Pletaal Tablet 50 mg)	
	Mean	SD	Mean	SD
AUC (ng.h.mL ⁻¹)	7315.98	2230.48	6744.48	2448.84
C_{max} (ng.mL ⁻¹)	729.02	192.49	545.3	166.85

n = 21 subjects

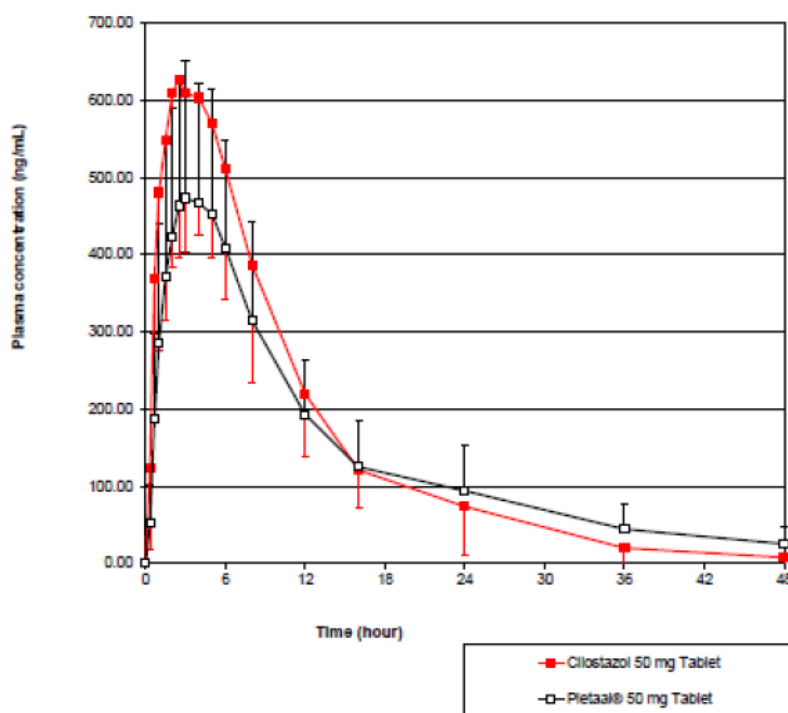


Figure 2. Mean plasma concentration profiles of Cilostazol 50 mg (Formula-1) vs. Pletaal 50 mg (Otsuka) in human volunteers (n=21)

Table 4. Statistical summary of AUC_t and C_{max} for Cilostazol 50 mg (Formula-1) vs. Pletaal 50 mg (Otsuka)

Parameter	%Ratio of Geometric Means (T/R)	90% Confidence Interval (T/R)		%CV	Conclusion
		Lower Limit	Upper Limit		
AUC (ng.h.mL ⁻¹)	109.9	102.43	117.9	13.22%	Bioequivalent *)
C _{max} (ng.mL ⁻¹)	133.93	124.21	144.41	14.17%	

*) Bioequivalence criteria (90%CI): 80.00 - 125.00%

Development of discriminating dissolution method

Cilostazol exhibits pH-dependent solubility. It was found that the lowest solubility of Cilostazol occurs in an acidic environment (Min et al. 2024). The medium with the lowest solubility was expected to be more effective in highlighting the sensitivity of the formulation. Another consideration was that at low pH the Cilostazol dissolves poorly (in the stomach), thus matching with in vivo absorption pattern and may provide strong in-vitro-in-vivo correlation. Therefore, the development of a discriminating method was studied using a pH 1.2 buffer medium. Other parameters that can be modified for the development of discriminating method are surfactant concentration, medium

volume, and agitation speed (Jangla and Raut 2024; Bredael et al. 2015; Lagace et al. 2004). By adjusting the parameter mentioned before, we made a new dissolution condition as shown in Table 5.

A comparative dissolution profile study was conducted for the bioequivalence batch (Formula-1) based on the new dissolution method design and summarized in Table 6. The appropriate dissolution method is expected to yield a profile similar to that observed in the previous pharmacokinetics study (Table 3 and Figure 2), where the Formula-1 sample exhibits higher drug release compared to the Pletaal tablet 50 mg.

A good agreement between the pharmacokinetic study and dissolution result was achieved by design E (although the f_2 result was slightly more than 50), where the Formula-1 sample exhibited a higher drug release profile than Pletaal. In this study, Design E demonstrated that reducing the surfactant concentration enhanced the discriminatory power of the dissolution method,

consistent with literature recommendations (Jangla and Raut 2024). Additionally, the use of lower paddle speeds and smaller dissolution volumes further contributed to method discrimination, aligning with previously reported findings (Bredael *et al.* 2015; Lagace *et al.* 2004). Therefore, method E was chosen as the dissolution method to predict the bioavailability of the sample.

Table 5. The new design of dissolution medium

Design	Medium	Apparatus	Volume	Rate	Sampling time (minutes)
Design A	pH 1.2 Buffer with 0.20% SLS	Type II USP (Paddle)	900 mL	75 rpm	5, 10, 15, 30, 45, 60
Design B	pH 1.2 Buffer with 0.30% SLS	Type II USP (Paddle)	900 mL	75 rpm	5, 10, 15, 30, 45, 60
Design C	pH 1.2 Buffer with 0.15% SLS	Type II USP (Paddle)	900 mL	50 rpm	5, 10, 15, 30, 45, 60
Design D	pH 1.2 Buffer with 0.10% SLS	Type II USP (Paddle)	500 mL	50 rpm	5, 10, 15, 30, 45, 60
Design E	pH 1.2 Buffer with 0.05% SLS	Type II USP (Paddle)	500 mL	50 rpm	5, 10, 15, 30, 45, 60

Table 6. Dissolution results of the new discriminating medium trial

Time (min)	Design A		Design B		Design C		Design D		Design E	
	Formula-1	Pletaal Tablet 50 mg (BN: TA8946)	Formula-1	Pletaal Tablet 50 mg (BN: TA8946)	Formula-1	Pletaal Tablet 50 mg (BN: TA8946)	Formula-1	Pletaal Tablet 50 mg (BN: TA8946)	Formula-1	Pletaal Tablet 50 mg (BN: TA8946)
5	27	33	22	41	20	22	18	22	11	9
10	54	50	50	59	37	33	38	37	22	15
15	65	61	64	71	46	44	49	47	27	17
30	77	79	80	87	57	61	60	65	28	21
45	85	89	84	94	63	70	70	75	30	23
60	87	94	88	97	67	76	82	82	32	24
f_2	70		48		69		73		57	

Development of modified formulation: In vitro study and pharmacokinetic evaluation

Since the dissolution method E has shown a similar profile to the pharmacokinetic result, it can be concluded that Formula-1 gives a higher drug release profile compared to the Pletaal tablet 50 mg. Therefore, the Formula-1 should be modified to achieve comparable results, especially for in vitro dissolution, before proceeding to a bioequivalence study. Based on available literature (Jinno *et al.* 2008), it was demonstrated that the bioavailability of the sample was increased when using a smaller particle size. In this literature particle size used was 44 μm . Since the Formula-1 sample particle size was only 8 μm , this fact

supports the pharmacokinetic data, which show that the Formula-1 sample has a higher release profile than the Pletaal tablet 50 mg. The modified formula was developed using Cilostazol API with a target particle size of 44 μm . The modified formula (Formula-2) was studied using the modified dissolution method (Design E) for a comparative dissolution study, with the results presented in Table 7. The result has shown that the similarity factor between the results of the Formula-2 sample and the Pletaal tablet 50 mg was 91, indicating similarity for the in vitro study. The increasing f_2 result between Formula-1 and Formula-2 in Table 7 also showed that the formula has significantly

improved, despite the study using a different batch of Pletaal tablet 50 mg.

Other dissolution media were also evaluated, although they are not considered biorelevant or discriminating media and are intended to meet

regulatory requirements. The results are summarized in Table 8. The similarity factors for medium water, buffer pH 4.5, and buffer pH 6.8 are, respectively, 58, 77, and 73, and were considered as similar results for the in vitro study.

Table 7. Comparative dissolution results of Formula-1 and Formula-2

Time (minutes)	0.05% SLS in pH 1.2 (Using method E)			
	Pletaal Tablet 50 mg (BN: TA8946)	Formula-1	Pletaal tablet 50 mg BN: TC9248	Formula-2
5	9	11	12	10
10	15	22	15	15
15	17	27	18	17
30	21	28	21	20
45	23	30	22	21
60	24	32	24	22
<i>f</i> ₂	57		91	

Table 8. Comparative dissolution results of Formula-2 in other media

Time (minutes)	Water +0.3% SLS (Paddle, 75 rpm, 900 mL) (QC release medium)		pH 4.5 + 0.15% SLS (Paddle, 75 rpm, 900 mL)		pH 6.8 +0.15% SLS (Paddle, 75 rpm, 900 mL)	
	Pletaal BN: TC9248	Formula-2	Pletaal BN: TC9248	Formula-2	Pletaal BN: TC9248	Formula-2
5	49	42	34	31	40	37
10	68	61	48	45	54	51
15	78	71	54	53	64	61
30	93	86	69	66	79	75
45	98	91	76	73	87	83
60	100	94	81	78	92	88
<i>f</i> ₂	58		77		73	

Table 9. Pharmacokinetic parameters (AUC and C_{max}) of Cilostazol 50 mg (Formula-2) vs. Pletaal 50 mg (Otsuka)

Parameter	Test Drug (Formula-2)		Comparator Drug (Pletaal 50 mg)	
	Mean	SD	Mean	SD
AUC (ng.h.mL ⁻¹)	407.71	104.46	459.76	120.57
C _{max} (ng.mL ⁻¹)	4746.98	1333.65	5265.21	1799.38

n = 24 subjects

Table 10. Statistical summary of AUC_t and C_{max} for Cilostazol 50 mg (Formula-2) vs. Pletaal 50 mg (Otsuka)

Parameter	%Ratio of Geometric Means (T/R)	90% Confidence Interval (T/R)		%CV	Conclusion
		Lower Limit	Upper Limit		
AUC (ng.h.mL ⁻¹)	91.45	86.52	96.66	11.22	Bioequivalent *)
C _{max} (ng.mL ⁻¹)	88.47	80.05	97.78	20.39	

*) Bioequivalence criteria (90%CI): 80.00 - 125.00%

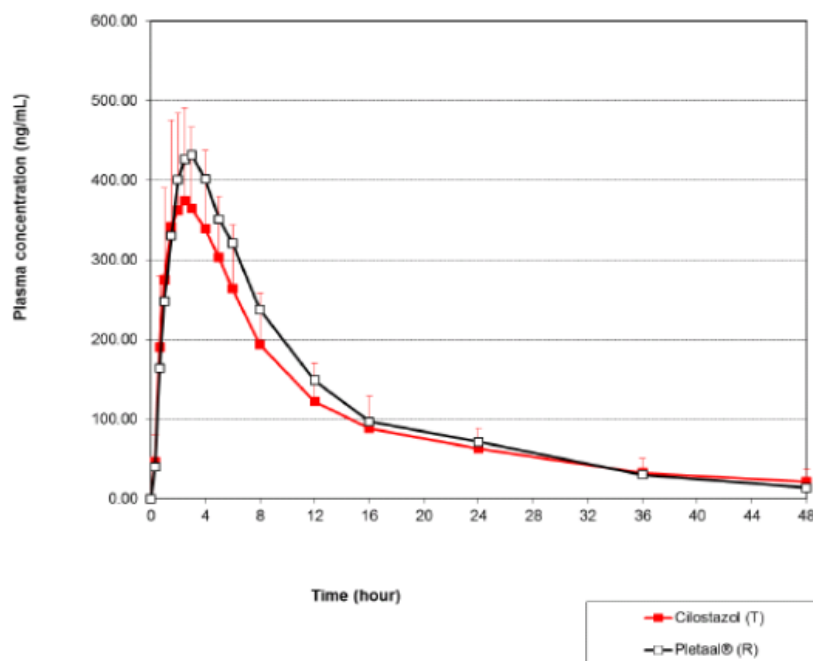


Figure 3. Mean plasma concentration profiles of Cilostazol 50 mg (Formula-2) vs. Pletaal 50 mg (Otsuka) in human volunteers (n=24)

The modified formula (Formula-2) was assessed for the pharmacokinetic evaluation with Pletaal tablet 50 mg. Pharmacokinetic results are presented in Table 9 and 10, along with the corresponding profile in Figure 3. The bioequivalence study showed that the AUC and C_{max} of Formula-2 result are bioequivalent to Pletaal within the specification range. From this perspective, it can be concluded that the dissolution method using a pH 1.2 Buffer with 0.05% SLS, a paddle speed of 50 rpm, and a dissolution volume of 500 mL is suitable as a discriminative dissolution method that was capable of predicting in vivo results.

CONCLUSION

The discriminating dissolution method for the BCS Class II Cilostazol tablet has been developed. The optimized method employed a pH 1.2 buffer containing 0.05% SLS, with a paddle speed of 50 rpm and a dissolution volume of 500 mL. The final method showed a dissolution profile that correlated with the pharmacokinetics results of Formula-1 and Pletaal tablet 50 mg as the comparator product. As the initial formula did not

meet the bioequivalence criteria, further optimization of the formula was achieved by modifying the API particle size, resulting in the final formula (Formula-2). The evaluation of Formula-2 using the developed dissolution method demonstrated a similar dissolution profile to the comparator product. Moreover, the pharmacokinetic analysis showed that the Formula-2 sample was bioequivalent compared to the comparator product. These results establish a discriminative dissolution method that reliably predicted the in vivo results for the Cilostazol tablet.

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REFERENCES

Bibi M, Din F ud, Anwar Y, Alkenani NA, Zari AT, Mukhtiar M, Abu Zeid IM, Althubaiti EH, Nazish H,

- Zeb A, Ullah I, Khan GM, Choi HG, 2022, Cilostazol-loaded solid lipid nanoparticles: Bioavailability and safety evaluation in an animal model, *J Drug Deliv Sci Technol* 74, doi: 10.1016/j.jddst.2022.103581.
- Bredael GM, Liang S, Hahn D, 2015, A strategy for quality control dissolution method development for immediate-release solid oral dosage forms, *Dissolution Technol* 22(3):10–16, doi: 10.14227/DT220315P10.
- Jangla P, Raut R, 2024, Selection and Parameters Affecting Dissolution Media, *Dissolution Technol* 31(2):78–84, doi: 10.14227/DT310224P78.
- Jinno JI, Kamada N, Miyake M, Yamada K, Mukai T, Odomi M, Toguchi H, Liversidge GG, Higaki K, Kimura T, 2008, In vitro-in vivo correlation for wet-milled tablet of poorly water-soluble cilostazol, *J Control Release* 130(1):29–37, doi: 10.1016/j.jconrel.2008.05.013.
- Kamada N, Yamada K, Mukai T, Odomi M, Ogawara K, Kimura T, Higaki K. 2009. IVIVC for oral absorption of cilostazol, a BCS class II drug, based on GITA (GI-transit-absorption) model, Paper Presented at: 24th JSSX Annual Meeting in Kyoto, Kyoto, Japan.
- Kherallah RY, Khawaja M, Olson M, Angiolillo D, Birnbaum Y, 2022, Cilostazol: a Review of Basic Mechanisms and Clinical Uses, *Cardiovasc Drugs Ther* 36(4):777–792, doi: 10.1007/s10557-021-07187-x.
- Lagace M, Gravelle L, di Maso M, McClintock S, 2004, Developing a discriminating dissolution procedure for a dual active pharmaceutical product with unique solubility characteristics, *Dissolution Technol* 11(1):13–17, doi: 10.14227/DT110104P13.
- Min KA, Kim NY, Jin MJ, Kim D, Ma Y, Karna S, Park YJ, 2024, In Vitro/In Vivo Correlation of Two Extended-Release Cilostazol Formulations, *Pharmaceuticals* 17(6):1–16, doi: 10.3390/ph17060787.
- Schrör K, 2002, The pharmacology of cilostazol, *Diabetes Obes Metab* 4(SUPPL. 2):14–19, doi: 10.1046/j.1463-1326.2002.0040s2s14.x.
- Shah VP, Lesko LJ, Fan J, Fleischer N, Handerson J, Malinowski H, Makary M, Ouderkirk L, Bay S, Sathe P, Singh GJP, Tillman L, Tsong Y, Williams RL, 1997, FDA guidance for industry 1 dissolution testing of immediate release solid oral dosage forms. *Dissolution Technol*, 4(4):15–22, doi: 10.14227/DT040497P15.
- Toyobuku H, Tamai I, Ueno K, Tsuji A, 2003, Limited influence of P-glycoprotein on small-intestinal absorption of cilostazol a high absorptive permeability drug, *J Pharm Sci* 92(11):2249–2259, doi: 10.1002/jps.10490.
- United States Pharmacopeia. 2025a. Cilostazol Tablets.
- United States Pharmacopeia. 2025b. Buffer Solutions.