INDONESIAN JOURNAL OF LIFE SCIENCES

RESEARCH ARTICLE

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Comparative Dissolution Profiles of Branded versus Generic Clopidogrel Bisulfate: Assessing *In Vitro* Bioequivalence

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ARTICLE INFO

Article history:

Submitted December 17, 2024
Revised August 21, 2025
Accepted September 10, 2025

DOI: 10.54250/ijls.v7i02.233

KEYWORDS:

Bioequivalence, Clopidogrel bisulfate, Dissolution profile, Generic and branded

HIGHLIGHTS

- Generic clopidogrel tablets demonstrated a faster dissolution rate at pH 1.2 compared to the branded formulation, while both displayed similar dissolution profiles at pH 4.5 and 6.8
- The generic formulation met the acceptance criteria for most parameters, except for thickness and hardness, which differed from the reference product, Plavix
- These findings support the generic product as a viable and effective alternative to the branded formulation

ABSTRACT

Clopidogrel, an antiplatelet agent widely prescribed for thromboembolic disorders, holds a substantial market presence in Indonesia. The branded form, Plavix (Sanofi, France), remains a clinical standard for such conditions; however, its high cost limits accessibility, driving reliance on generic alternatives. In pharmaceutical evaluation, branded formulations serve as a standard reference for assessing the quality, efficacy, and dissolution performance of generic products. This study compared the dissolution profile and physical properties of generic clopidogrel bisulfate tablets manufactured by PT Phapros TBK with the branded reference licensed by Sanofi. Quality attributes, including weight and size uniformity, hardness, and disintegration time, were assessed as per the Indonesian Pharmacopoeia (6th edition) standards. Dissolution tests were conducted at pH levels of 1.2, 4.5, and 6.8, with 12 replicates per interval. Results revealed that the generic and branded clopidogrel exhibited significantly different dissolution profiles at pH 1.2, but demonstrated similar profiles at pH 4.5 and 6.8. These findings are expected to offer valuable insights into the interchangeability of generic and branded clopidogrel in Indonesia, as well as their potential clinical implications in a high-demand market.

INTRODUCTION

The pharmaceutical industry in Indonesia plays a crucial role in supporting and maintaining public health, but it still heavily relies on importing raw materials from foreign countries. This dependence on foreign suppliers can negatively impact the nation's resilience. To address this issue, the Indonesian National Agency of Drug and Food Control (BPOM) has implemented various policies to promote the use of domestically produced drug raw materials. These initiatives encompass incentives and facilities for pharmaceutical companies that utilize local raw materials, as well as investing in research and development to improve the quality of domestic raw materials. In 2022, BPOM issued a decree aimed at increasing the utilization of domestically produced raw materials in pharmaceutical preparations. One such example of a locally produced raw material is clopidogrel bisulfate from Kimia Farma Sungwun Pharmacopia (KFSP) (BPOM, 2018; Tawfik et al., 2022).

Despite being the most consumed drug in Indonesia, with a total consumption value of IDR 4.52 trillion according to internal data from BPOM, clopidogrel's pharmaceutical production still heavily relies on imported active ingredients from other countries. Clopidogrel is an antiplatelet medication used to treat thromboembolic disorders. It inhibits platelet aggregation mediated by adenosine diphosphate and is commonly prescribed as an alternative to aspirin for patients at risk of cardiovascular events such as myocardial infarction, peripheral arterial disease, and stroke (Eikelboom et al., 2012). Administration of clopidogrel happens orally as bisulfate, with its dose equivalent to 75 mg expressed in base form. It is rapidly but incompletely absorbed after oral administration, undergoing hepatic metabolism via specific cytochrome P450 enzymes, primarily CYP3A4 and CYP2B6, which produce a thiol derivative as the active metabolite (Jiang et al., 2015).

In industries, dissolution test is an essential physical method used to assess the uniformity of a drug formulation by measuring the rate at which the API is released and dissolved from the preparation (Alburyhi et al., 2024). It ensures quality control during the production process and verifies the *in vitro* bioequivalence between different batches of the product (Farfan et al., 2020). On the other hand, BPOM (2022) defines Comparative Dissolution Test or *Uji Disolusi Terbanding* as a method to assess the similarity in dissolution profiles between a test drug and its comparator, typically a reference product available in the market. This test is crucial for ensuring that generic drugs have a similar release rate of active substances to the reference product, thereby confirming bioequivalence (Farfan et al., 2020).

Clopidogrel, classified as a Class II drug according to the Biopharmaceutical Classification System (BCS), is an antiplatelet medication with low water solubility that possesses the ability to penetrate cell membranes. This classification indicates that it has a high absorption rate but a slow breakdown rate. In evaluating drug equivalence, the dissolution test plays a crucial role, as it measures the rate at which the active ingredient is released from the tablet into the body. This test helps compare the release profiles of the reference drug (branded) and the test drug (generic). By ensuring that the dissolution profiles of both drugs are similar, the test confirms that the generic version will release the active ingredient at the same rate as the branded drug. As a result, this comparison is essential in preserving the desired therapeutic effect, efficacy, and bioequivalence of the test product; ensuring that it provides the same clinical benefits as the branded product (BPOM, 2022).

For this study, the dissolution profile and physical properties of the generic clopidogrel bisulfate produced locally in PT Phapros Tbk were compared with those of the branded clopidogrel bisulfate extracted from another company in Indonesia under license from Sanofi in France. Other physical property measurements, including weight and size uniformity, hardness, and the disintegration test, were also conducted. The results of each parameter were compared to the acceptance criteria specified in the 6th

edition of Farmakope Indonesia (FI). From this, the study sought to provide evidence supporting the bioequivalence of generic and branded clopidogrel bisulfate tablets.

MATERIALS AND METHODS

Materials and equipments

The materials listed include a working standard of clopidogrel bisulfate, which is a chemical substance used as a benchmark to assess the genuineness and quality of clopidogrel, hydrochloric acid (HCl) (Merck, Germany), sodium acetate (Sigma-Aldrich, Germany), acetic acid (Merck, Germany), potassium dihydrogen phosphate (KH_2PO_4) (Merck, Germany), sodium hydroxide (NaOH) (Merck, Germany), aqua pro injection, clopidogrel tablets made with KFSP raw material (Phapros, Indonesia), and clopidogrel tablets made with imported raw material that utilize raw materials sourced from overseas and Plavix (Sanofi, France), a trademark associated with clopidogrel. All materials were provided by PT. Phapros Tbk.

The equipment listed consists of an analytical balance used for accurately measuring mass, beaker glass utilized for mixing and storing chemicals, measuring flask employed for precise measurement of liquid volume, funnel for transferring substances, stirring rod for mixing purposes, measuring glass for determining liquid volume, test tube for holding and heating small amounts of substances, test tube rack for organizing test tubes, drying cabinet for moisture removal, durapone PVDF membrane filter for filtration, dissolution testing apparatus for evaluating dissolution rate, and Ultraviolet-visible (UV-Vis) spectrophotometer (Shimadzu, Japan) for measuring the absorption or transmission of light. All of the equipment was provided by PT. Phapros Tbk.

Methods

Tablet parameters

All tests for clopidogrel bisulfate tablets, including size uniformity, weight uniformity, hardness, moisture content, disintegration time, and dissolution, were conducted according to the FI 6th Edition. For size uniformity, the thickness and diameter of 10 tablets were measured using a vernier caliper and averaged to get the mean value of all 10 tablets. Weight uniformity was assessed by weighing 30 tablets and calculating the percentage deviation from the mean to ensure compliance with specified limits. Hardness was measured using a tablet hardness tester, and disintegration time was evaluated by placing tablets in a water bath at 36.5–37.5°C until disintegrated (FI, 2020).

To detect the assay of a tablet, a standard solution of 75 mg of clopidogrel was prepared in 50 mL of methanol, filtered through a 0.45 µm microfilter, and compared with the test solution from 20 tablets. Both generic and branded forms of clopidogrel were analyzed using HPLC (Waters, USA) with UV detection at 220 nm using a specific column (L57, 150 x 4.6 mm, 5 µm) with a mobile phase consisting of a phosphate buffer solution and acetonitrile to determine the percentage of the active pharmaceutical ingredient (API). Meanwhile, during the dissolution testing, the release of the API was evaluated exclusively using a UV–visible spectrophotometer equipped with a fixed-wavelength detector operating at 240 nm. Each tablet was placed into a dissolution flask filled with a buffer containing HCl of pH 2. The sample filtrate was then taken after 30 minutes and measured using the UV-vis spectrophotometer at 240 nm with a media blank. To extend the comparative assessment across physiologically relevant conditions, dissolution studies were performed at pH values of 1.2, 4.5, and 6.8. For pH 1.2, 8.3 mL of 37% HCl was mixed with one liter of purified water. At pH 4.5, 1.8 g of sodium acetate was dissolved in 0.95 L of purified water, and the pH was adjusted with acetic acid. Lastly, in pH 6.8, 6.8 g of KH_2PO_4 and 0.9 g of NaOH were dissolved in 0.95 L of purified water, with the pH adjusted using NaOH or H_3PO_4 (FI, 2020).

For these media, the linearity of the clopidogrel bisulfate stock solution was assessed by dissolving the working standard in methanol to create a homogeneous solution. A series of stock solutions was prepared by pipetting 1.0, 2.0, 3.0, 4.0, 5.0, and 6.0 mL of the stock solution into separate 50.0 mL volumetric flasks. These solutions were then diluted with dissolution media and shaken until homogeneous. The absorbance of these solutions was measured at 240 nm using a UV spectrophotometer against a dissolution media blank. In the sample solution test, dissolution flasks containing media at three pH levels were heated, and a tablet of either the test or comparator product was added. The apparatus was immersed and rotated at 50 rpm, with 11 mL samples collected at intervals (5, 10, 15, 30, 45, and 60 minutes), resulting in Solution S. This solution was then diluted with dissolution media, resulting in Solution S1. To ensure clarity, Solution S was filtered using Durapore PVDF or RC 0.45 µm membrane filter, and the absorbance of the sample was measured at 240 nm against a blank of the dissolution medium. For pH 1.2, the apparatus was withdrawn, and the HCl 0.1N dissolution media was replaced with an acetate buffer at pH 4.5 (FI, 2020).

Data analysis

A bioequivalence (BE) study of generic and branded clopidogrel bisulfate was assessed using the model-independent method, with calculations based on the difference factor *f1* (Eq. 1) and similarity factor *f2* (Eq. 2) values outlined in the BPOM (2022) guidelines. If the *f1* and *f2* values meet the required criteria, it can be concluded that both the generic and branded clopidogrel bisulfate tablets have equally good quality control. The formulas for *f1* and *f2* are provided in the following equations:

$$f_1 = \left[\frac{\sum_{t=1}^{n} \left| R_t - T_t \right|}{\left[\sum_{t=1}^{n} R_t \right]} \right] \times 100 \quad (1)$$

$$f_2 = 50 \times log\left\{ \left[1 + \left(\frac{1}{n} \right) \sum_{t=1}^{n} (R_t - T_t)^2 \right]^{-.05} \times 100 \right\} \quad (2)$$

In both formulas, R_t refers to the percentage of the drug dissolved from the reference product at a specific time point *t*, while T_t represents the percentage dissolved from the test product at the same time point. The symbol *n* denotes the total number of sampling time points during the dissolution study. Factor *f1* measures the relative error between two dissolution curves, with values typically ranging from 0 and 15. Factor *f2* assesses the closeness of 2 profiles, with values ranging from 50 and 100. Based on established regulatory standards, an *f2* value ≥ 50 indicates that the dissolution profiles of the test and reference products are equivalent. This suggests similar drug release characteristics for both formulations (Sirait et al., 2020).

Statistical analysis

All statistical analyses in this study were performed using the GraphPad Prism v.8.0.1 software. The mean and standard deviation values obtained from each of the two products were differentiated using an unpaired t-test in different rows. Meanwhile, the normality of data was evaluated using the Shapiro–Wilk test. A two-tailed significance level of $\alpha = 0.05$ was used, with a 95% confidence criterion, and results were deemed statistically significant if $p < 0.05$.

RESULTS

Physical and chemical parameters

Both generic and branded clopidogrel bisulfate share similar traits in terms of their color, shape, taste, smell, and texture **(Table 1)**. However, there is a minor difference in the composition of active ingredients and excipients between the two. Despite these differences in excipients, both versions of clopidogrel require storage at a temperature below 30°C and should be shielded from light and moisture to maintain their quality and effectiveness (FI, 2020).

Table 1. Comparative overview of generic and branded clopidogrel bisulfate, including estimated excipient composition.

Description	Generic Clopidogrel Bisulfate	Branded Clopidogrel Bisulfate (Plavix)
Color	Pink	Pink
Shape	Round and convex in shape	Round and convex in shape
Expired date	3 years	3 years
Composition	Each film-coated tablet contains 97.88 mg of clopidogrel bisulfate, which is equivalent to 75.0 mg of clopidogrel	Each film-coated tablet contains 75 mg of clopidogrel (as bisulfate)
Excipients	**Core:**	
	Lactose monohydrate Low Hydroxypropyl cellulose Colloidal silicon dioxide Sodium stearyl fumarate	Hydrogenated castor oil Low Hydroxypropyl cellulose Mannitol Microcrystalline cellulose Polyethylene glycol 6000
	Coating:	
	Hypromellose 2910 Titanium dioxide Triacetin Polyethylene glycol 6000 FD&C Red/Allura Red AC	Ferric oxide Hypromellose 2910 Lactose monohydrate Titanium dioxide Triacetin Carnauba wax
Storage	Store at a temperature below 30°C, protected from light and moisture	Store at a temperature below 30°C.

Further details on the physical characteristics of the generic and branded clopidogrel tablets, are presented in **Table 2**. These parameters were analyzed by calculating the average and coefficient of variation (CV) values, which are compared against standards outlined in the 6th edition of the FI.

Table 2. Physical profiles of generic and branded clopidogrel bisulfate

Parameters	Generic Clopidogrel Bisulfate		Branded Clopidogrel Bisulfate (Plavix)	
	Average	CV (%)	Average	CV (%)
Diameter	8.64 mm	0.31	8.69 mm	0.39
Thickness	4.36 mm	0.70	4.00 mm	2.07
Hardness	13.88 kp		10.55 kp	
Disintegration time	3 minutes 33 seconds		10 minutes 42 seconds	
Weight	269.52 mg	0.62	256.82 mg	2.06
Moisture Content	1.22 %		1.71 %	
Weight Variation	Acceptance value = 1.5 %		Acceptance value = 3.1 %	

As the key determinants of bioequivalence, chemical profile tests such as dissolution and assay results were analyzed separately, as shown in **Table 3**.

Table 3. Chemical profiles of generic and branded clopidogrel bisulfate

Parameters	Generic Clopidogrel Bisulfate			Branded Clopidogrel Bisulfate (Plavix)		
	Minimum 85 % (Q= 80 %) for 30 mins			Minimum 85 % (Q= 80 %) for 30 mins		
Dissolution	103	100	102	85	100	90
	100	100	100	101	100	95
Assay	98.1 %			99.8 %		

Dissolution testing evaluates how effectively the API is released from a tablet into a controlled dissolution medium under specific conditions. This test is crucial for determining the drug's release pattern, which in turn influences its bioavailability, therapeutic effect, and overall efficacy. For clopidogrel, the regulatory acceptance criteria specify that at least 85% of the API should dissolve within 30 minutes, with the initial dissolution point requiring at least 80% API to be released. Both versions of clopidogrel met these criteria, showcasing their consistent and effective API release within the allotted timeframe (FI, 2020).

The assay of a drug quantitatively determines the purity, potency, and concentration of its API, ensuring compliance with quality standards. For clopidogrel bisulfate, the acceptable assay range is set between 90% and 110%. Both the generic and branded formulations delivered assay values within this range, confirming their potency, compliance with regulatory standards, and reliability in providing the intended therapeutic effects (FI, 2020).

Comparative dissolution test

The *f1* and *f2* values for generic and branded clopidogrel bisulfate tablets in dissolution media with varying pH levels are presented in **Table 4**, where an *f2* value of at least 50 confirms comparable quality and dissolution performance between the formulations. This threshold adheres to EMA and FDA recommendations as the most prevalent model-independent approach and is regarded as a tolerable indicator of similarity profile (Gomez et al., 2022).

Table 4. Similarity factor (*f1* and *f2*) values of generic and branded clopidogrel bisulfate at different pH conditions

pH	*f1*	*f2*	Description
	Criteria : 0 - 15	**Criteria: 50 - 100**	
1.2	24.03	33.58	Different for f*1* & f*2*
4.5	30.12	50.93	Different for f*1* & Similar for f*2*
6.8	27.91	55.01	Different for f*1* & Similar for f*2*

As presented in **Table 4**, the dissolution profiles of the two products at pH 1.2 differ significantly, as the *f1* and *f2* values fall outside the acceptable similarity criteria. The *f1* value of 24.03 exceeds the permissible range of 0-15, while the f2 value of 33.58 is below the required threshold of 50. This indicates that at pH 1.2, the generic clopidogrel does not exhibit dissolution behavior similar to the branded version.

In contrast, the results at pH 4.5 indicate improved alignment between the two formulations. The *f2* value of 50.93 meets the acceptable criteria of 50-100, suggesting that the dissolution profiles of the generic and branded clopidogrel are comparable at this pH. When the *f2* value falls within the 50-100 range, it confirms similarity in the dissolution characteristics of both products (Farfan et al., 2020). Thus, at pH 4.5, the two versions of clopidogrel bisulfate display similar dissolution behaviors.

Lastly, the results at pH 6.8 closely resemble those obtained at pH 4.5. The *f2* value of 55.01 falls within the acceptable range of 50-100, demonstrating that the dissolution profiles of the two formulations are sufficiently similar. This indicates that both versions of clopidogrel exhibit comparable dissolution behavior or patterns at pH 6.8.

Before comparative analysis, the raw data, although confidential from the dissolution test, were evaluated for normality. Upon analysis, this data fully met its required assumptions ($p \geq 0.05$) and were subsequently analysed with a parametric t-test for each successive pH conditions **(Table 5-7)**.

Table 5. Statistical t-test of generic and branded clopidogrel bisulfate in simulated acidic medium (pH 1.2)

pH 1.2				
Time (min)	**Mean±SD (Generic)***	**Mean±SD (Branded)***	**p-value**	**Significant (p<0.05)**
5	34.56±6.66	21.42±4.78	<0.0001 ****	Yes
10	85.69±11.26	49.92±8.71	<0.0001 ****	Yes
15	99.06±1.32	70.76±10.59	<0.0001 ****	Yes

Time (min)	Mean±SD (Generic)*	Mean±SD (Branded)*	p-value	Significant (p<0.05)
30	99.54±1.33	96.71±6.91	0.1782	No
45	100.1±1.05	98.05±3.77	0.3302	No
60	100.2±1.64	99.32±2.73	0.3663	No

*Mean derived from 12 replication with 12 tablets for each time interval.

Table 6. Statistical t-test of generic and branded clopidogrel bisulfate in simulated acetate buffer medium (pH 4.5)

pH 4.5				
Time (min)	**Mean±SD (Generic)***	**Mean±SD (Branded)***	**p-value**	**Significant (p<0.05)**
5	14.910±2.75	5.960±2.01	<0.0001 ****	Yes
10	33.648±3.36	16.729±3.66	<0.0001 ****	Yes
15	37.342±4.03	24.790±4.23	<0.0001 ****	Yes
30	37.298±4.12	33.933±4.10	0.0574	No
45	37.685±4.11	35.409±3.23	0.1457	No
60	38.487±3.95	36.394±2.97	0.1565	No

*Mean derived from 12 replication with 12 tablets for each time interval.

Table 7. Statistical t-test of generic and branded clopidogrel bisulfate in simulated phosphate buffer medium (pH 6.8)

pH 6.8				
Time (min)	**Mean±SD (Generic)***	**Mean±SD (Branded)***	**p-value**	**Significant (p<0.05)**
5	10.528±3.16	4.290±1.50	<0.0001 ****	Yes
10	26.121±3.01	10.830±2.76	<0.0001 ****	Yes
15	28.411±2.90	18.534±3.66	<0.0001 ****	Yes
30	28.666±2.96	27.566±3.21	0.3923	No
45	28.832±2.65	29.148±2.92	0.784	No
60	29.134±2.65	29.871±2.92	0.524	No

*Mean derived from 12 replication with 12 tablets for each time interval.

To better contextualize these findings and get a clear picture of their dissolution profiles, the means of drug dissolved across all 3 pH conditions were plotted in **Figure 1**, highlighting the overall trend and release patterns between the two formulations.

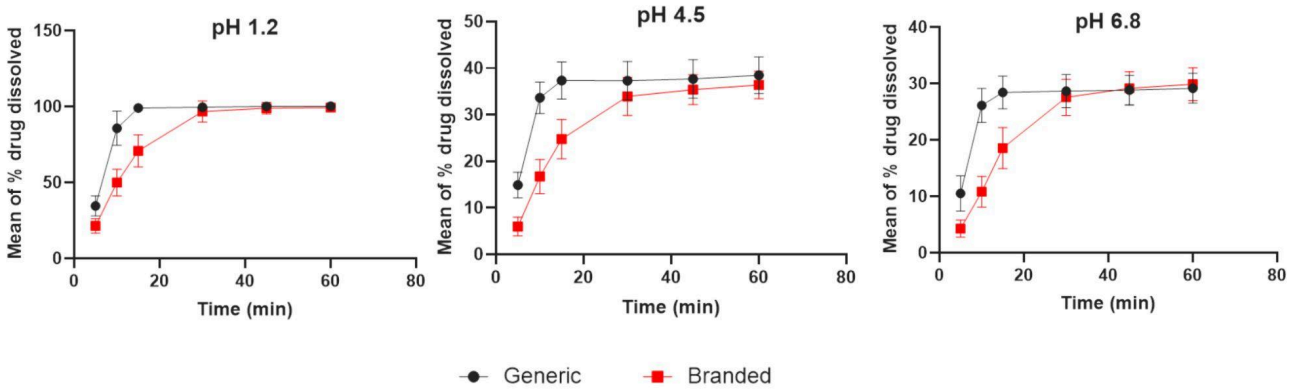

Figure 1. Dissolution profile of generic and branded clopidogrel bisulfate in pH 1.2 (left), pH 4.5 (middle), and pH 6.8 (right). Error bars represent standard deviation from 12 replication with 12 tablets for each data point

DISCUSSION

Physical and chemical parameters

According to the internal specifications provided by Phapros, the acceptable range for tablet thickness and diameter is 8.5–8.8 mm and 4.2–4.4 mm respectively. The diameter results for both the generic and branded clopidogrel tablets fully met the criteria. However, the thickness of the branded tablet fell below the specified range. This could impact the drug's performance by introducing inaccuracies in dosage, altering disintegration properties, and affecting patient adherence (Adepu & Ramakrishna, 2021).

Other critical parameters, such as hardness, weight, disintegration time, moisture content, assay, and dissolution, are vital in ensuring the quality, safety, and efficacy of clopidogrel tablets. Hardness, for instance, is a measure of the force required to break a tablet when subjected to pressure. It is essential for maintaining the tablet's structural integrity during handling and ensuring appropriate dissolution and release characteristics (Abdul-Hasan, 2022). The internal hardness specification ranges between 11 and 19 kp. Testing revealed that while both products met this standard, the generic tablet demonstrated greater resistance to mechanical stress compared to the branded version (FI, 2020).

Disintegration is another essential parameter that ensures the timely release and absorption of the active ingredient. It measures the time it takes for a tablet to break down into smaller fragments for effective absorption into the bloodstream (Markl et al., 2021). According to PT Phapros internal standards, the maximum disintegration time should not exceed 15 minutes to guarantee optimal bioavailability and drug release. Testing revealed that both the generic and branded tablets disintegrated within this limit. However, the generic tablet exhibited a faster disintegration time, indicating a quicker onset of dissolution. Since clopidogrel is classified as a Class II drug, with solubility being a rate-limiting factor, a faster disintegration alone does not necessarily translate into a faster therapeutic effect (Markl et al., 2021).

Weight variation, like weight assessment, is a crucial parameter for evaluating the consistency of tablet production. While weight assessment measures the mass of individual tablets, weight variation focuses on the differences between the weights of tablets within a batch. This ensures that each tablet stays within an acceptable margin around the target weight, promoting batch uniformity (Kurashima et al., 2020). According to the specified standards, the acceptance value for weight variation among 10 tablets must not exceed 15%. Testing revealed that both the generic and branded clopidogrel tablets adhered to this standard, demonstrating uniformity and consistency in production across different batches (FI, 2020).

Moisture content (MC) is another critical parameter that quantifies the amount of water present in a drug, and is typically expressed as a percentage of the drug's total weight. Maintaining an optimal MC

ensures that the drug remains chemically stable and free from microbial contamination, contributing to its safety and efficacy for patients (Sirait et al., 2020). The ideal MC for tablets is generally below 2% of their total weight. Both the generic and branded formulations of clopidogrel complied with this standard, confirming their stability and ideal physical properties (FI, 2020).

Comparative dissolution test

The comparative dissolution test aims to evaluate the influence of formulation and manufacturing processes on the dissolution profiles of a drug. This test serves as a preliminary assessment for estimating the bioavailability and bioequivalence between the test product and the reference (comparator) product (BPOM, 2022).

Additionally, the comparative dissolution test is used to verify the similarity of the drug's quality and properties, even in cases where minor modifications have been made to the formulation or manufacturing process after the drug has received marketing approval. These guidelines are outlined by BPOM in their 2022 Guideline of Bioequivalent Test.

For this study, dissolution testing of both generic and branded clopidogrel bisulfate was conducted at three different pH levels. Sampling was performed at specific time intervals: 5, 10, 15, 30, 45, and 60 minutes, with 12 replicates for each time point. These time intervals were selected to capture the dissolution features of the drug at different stages throughout the test. Moreover, conducting 12 replicates for each time interval enhanced the credibility and precision of the findings by ensuring reliable and accurate results (Ali et al., 2018; FI, 2020).

At all tested pH conditions **(Table 5-7)**, the results were statistically different between the two formulations during the initial phase of the curve, specifically covering the 5- to 15-minute sampling mark ($p<0.0001$). In each of the cases, the generic version ended up releasing more drugs than Plavix. However, no significant difference was observed beyond 30 minutes, as seen by the plateauing shape in **Tables 5-7** (where $p > 0.05$) and illustrated in **Figure 1**. This plateau is generated as the system likely reaches its dissolution equilibrium state, either through the drug reaching its solubility limit or because most of the drug has already been released (Avdeef, 2012). Notably, both formulations ended up achieving >85% drug release at pH 1.2. Meanwhile, a lower drug release percentage was observed at pH 4.5 and pH 6.8, with approximately 38% and 29% dissolution, respectively. Needless to say, this testing alone does not provide a definitive conclusion as to which formulation exhibits a quicker therapeutic onset (FI, 2020).

Firstly, at pH 1.2, in a dissolution medium of 0.1 N HCl, the test product follows a rapid trend and dissolves more than 85% within 15 minutes, whereas the reference product required more than 30 minutes to reach the same dissolution level. The calculated *f2* was 33.58, indicating that the two products are not similar and can be considered different in their dissolution behavior under these conditions (FI, 2020).

Meanwhile, at pH 4.5, in a sodium acetate buffer medium, both the test product and the reference product dissolved less than 85% within 60 minutes. The *f2* was 50.93, meeting the criteria for similarity and suggesting that the dissolution profiles of the two products are comparable at this pH. Lastly, in a phosphate buffer medium at pH 6.8, both the test and reference products dissolved less than 85% within 60 minutes. The *f2* was 55.01, again meeting the criteria for similarity. This result indicates that at pH 6.8, the two products exhibit comparable dissolution behavior and are considered *similar* (FI, 2020).

In pH 1.2, the difference in dissolution profiles likely arises due to variations in formulation, particularly in the composition and functionality of the excipients. In this highly acidic medium, the generic clopidogrel exhibits a faster and more complete dissolution compared to the branded formulation. This faster dissolution is likely due to the presence of lactose monohydrate as the filler, which is highly

water-soluble and dissolves rapidly in acidic conditions. This promotes tablet disintegration by creating channels for water to penetrate and break apart the tablet matrix, facilitating the release of clopidogrel bisulfate (Goel et al., 2008). Additionally, the inclusion of sodium stearyl fumarate as a lubricant in the generic formulation further enhances water penetration and reduces hydrophobic interactions within the tablet. Unlike hydrophobic lubricants such as magnesium stearate, sodium stearyl fumarate's properties allow water to interact more easily with the tablet, accelerating the dissolution process (Al-Mohaya, 2018). On the other hand, the branded formulation relies on mannitol and microcrystalline cellulose as fillers. Mannitol dissolves more slowly in water, while microcrystalline cellulose is insoluble and forms a dense matrix. Both of which hinder rapid water infiltration and dissolution (Chaerunisaa et al., 2019).

Although differences in dissolution profiles remain evident, the generic formulation consistently outperforms the branded product across every pH level shown in **Figure 1**. Besides the presence of fillers, another potential factor contributing to this disparity is the variation in lubricants and coatings used in the formulations. The generic formulation includes sodium stearyl fumarate as a lubricant, which effectively reduces inter-particle friction and improves water penetration throughout the tablet matrix (Zhao et al., 2022). This property enhances powder flow and promotes faster disintegration of the tablet, particularly in acidic conditions (Blanco et al., 2021). In contrast, the branded formulation includes hydrogenated castor oil to provide its lubricant properties. For this formulation, Hydrogenated castor oil in the core primarily acts as a binder and a stabilizer, helping to improve the cohesion and integrity of the tablet. While it has some lubricating properties, these are generally less effective in promoting rapid water penetration compared to sodium stearyl fumarate. Its role in the core also affects the tablet's ability to disintegrate quickly in aqueous environments, leading to slower dissolution. Due to this, it does not significantly reduce inter-particle friction, which is the key role of a lubricant like sodium stearyl fumarate. This lack of lubrication can result in a denser tablet structure and slower disintegration, leading to a delayed dissolution compared to the generic formulation (de Backere et al., 2023).

Additionally, the composition of the tablet coatings further highlights critical differences between the two formulations. The generic formulation incorporates hypromellose 2910, titanium dioxide, triacetin, polyethylene glycol 6000, and FD&C Red/Allura Red AC as part of its coating. Hypromellose 2910 is a hydrophilic polymer that facilitates the controlled release and dissolution of the tablet by promoting water absorption (Ojstersek et al., 2023). Titanium dioxide serves as a coloring agent and opacifier, while triacetin is used as a plasticizer to enhance the flexibility of the coating (Anaya-Esparza et al., 2020). Polyethylene glycol 6000 (PEG 6000) is a hydrophilic polymer that readily interacts with water, facilitating faster water absorption and coating breakdown (Zhang et al., 2018). Meanwhile, FD&C Red/Allura Red AC functions primarily as a coloring agent and lacks significant moisture-protective or controlled-release properties that allow water to penetrate and dissolve the tablet. The hydrophilic nature of these components promotes quick water penetration and disintegration, thereby supporting faster dissolution of the generic formulation (Kwon et al., 2022).

On the other hand, the branded clopidogrel formulation employs a different coating combination, which includes ferric oxide, hypromellose 2910, lactose monohydrate, titanium dioxide, triacetin, and carnauba wax. Ferric oxide, a coloring agent, does not significantly impact dissolution. Hypromellose 2910 serves a similar role in both formulations, aiding in controlled release. Lactose monohydrate, used in the coating of the branded tablet, is a water-soluble excipient, but its effect is less pronounced in the outer coating compared to the tablet core (Janssen et al., 2022). Triacetin, similar to the generic formulation, acts as a plasticizer. PEG 6000 is incorporated into the tablet core rather than the coating. The key difference lies in the presence of carnauba wax and in the usage of PEG 6000. PEG 6000 is a hydrophilic polymer known for

its ability to interact with water, which enhances the tablet's disintegration and dissolution properties when dissolved in aqueous environments. When used in the core, PEG 6000 aids in the overall tablet breakdown by attracting water to the core and facilitating the release of the active ingredient (Gao et al., 2024). However, the use of PEG 6000 in the core, as opposed to the coating, does not directly contribute to the breakdown of the outer coating. The branded formulation's coating, which includes hydrophobic components such as carnauba wax, remains largely unaffected by PEG 6000. This is due to a protective barrier by hindering water penetration and delaying the release of the active ingredient. This in turn, contributes to a slower water penetration and a delayed dissolution profile compared to the generic formulation (Kaurav et al., 2024; Yu et al., 2017).

Lastly, the differences in dissolution profiles between the formulations could also be attributed to the varying percentages or amounts of excipients used in each formulation. Although the exact quantities are confidential, even slight differences in the proportion of water-soluble or hydrophobic excipients could significantly affect how quickly the tablets dissolve. The faster dissolution profile of the generic clopidogrel may be attributed to the optimized balance of excipients, such as the high solubility of lactose monohydrate and the presence of sodium stearyl fumarate, which collectively enhance water penetration and disintegration (van der Merwe et al., 2020).

At pH 4.5 and 6.8, the dissolution profile of the test product is classified as *similar* to the reference product. Under these conditions, both the test and reference products exhibit dissolution rates below 85% within a timeframe exceeding 60 minutes. This behavior is attributed to the low solubility of clopidogrel bisulfate at intestinal pH levels, as the drug is classified under the Biopharmaceutics Classification System (BCS) Class II. BCS Class II drugs are characterized by their high permeability and low solubility, which results in slower dissolution rates in the gastrointestinal tract (El-Laithy et al., 2018).

As a BCS Class II drug, the dissolution of clopidogrel bisulfate is the rate-determining step for its absorption. According to Jassim & Hussein (2017), drugs in this category have the potential for *In Vitro-In Vivo* Correlation (IVIVC), particularly when the dose is high and when the *in vitro* dissolution test closely mirrors the *in vivo* dissolution process. This explains the slower and comparable dissolution rates observed at pH 4.5 and 6.8, highlighting that both formulations exhibit similar performance under intestinal pH conditions.

Limitations

Several limitations were observed during the course of this experiment. Firstly, the absence of an *in vivo* study limits the ability to fully understand the behavior of the drug within the human body. While dissolution testing is a valuable tool for predicting *in vivo* behavior, definitive conclusions about the bioavailability and bioequivalence of the products require further *in vivo* studies. Secondly, optimizing the generic formulation of the clopidogrel bisulfate tablets to achieve consistent similarity in dissolution profiles across all three pH conditions (1.2, 4.5, and 6.8) is recommended. Such optimization could potentially improve the product's performance and ensure its behavior aligns more closely with the reference product *in vivo*. Lastly, further *in vivo* studies and IVIVC studies are needed to confirm the findings and provide a more accurate representation of the drug’s pharmacokinetics and bioequivalence in real-world conditions.

CONCLUSION

Based on this study, the generic clopidogrel bisulfate tablets produced locally by Phapros satisfied most of the acceptance criteria outlined in the Indonesian Pharmacopoeia (6th Edition), with exceptions in thickness and hardness that did not align with those of the reference product, Plavix. Dissolution testing

revealed a quicker release rate for the generic formulation, yielding an *f2* of 33.58, which was far below the regulatory acceptance criteria. This finding is particularly relevant because gastric dissolution constitutes the initial stage of clopidogrel release, and failure to demonstrate similarity at this point might carry implications, given that the regulatory authority's mandate similarity across all tested pH conditions. In contrast, at pH 4.5 and 6.8, the two formulations complied with regulatory guidelines, with *f2* values of 50.93 and 55.01, respectively, thereby meeting the acceptable criteria under these conditions. These findings suggest that although the generic formulation has potential as a comparable alternative to Plavix in the intestinal environment, its dissimilarity at gastric pH underscores a key limitation that needs to be addressed. Therefore, further formulation adjustments and *in vivo* bioequivalence studies are necessary to fully establish whether the generic drug can be substituted for Plavix.

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