

Post-market in vitro bioequivalence study of innovator and generic gefitinib tablets: evaluation of JKN medicine quality

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ABSTRACT: Gefitinib is one of the Tyrosine Kinase Inhibitors (TKIs), as first-line therapy for Non-Small Cell Lung Cancer (NSCLC) with positive EGFR mutation. Gefitinib started to be accommodated in Jaminan Kesehatan Nasional (JKN) insurance in 2015 with the innovator gefitinib and was replaced by a generic product in the middle of 2021. This research was conducted to see whether the quality of generic gefitinib equivalent to the innovator through a post-market in vitro bioequivalence test. The assay method refers to previous research by Sandhya et al 2013 with High Performance Liquid Chromatography (HPLC), while the dissolution test method is in accordance with the Food and Drug Association (FDA) 2010. We collected innovator from the official distributor and 3 batches (all batches that have been used in the JKN program) of generic products from hospitals where lung cancer therapy services were provided. We evaluated the dissolution profile with similarity and unsimilarity factors and assessed based on a standard specification of dissolution profile that was informed in the innovator's BPOM-approved brochure (average of 6 samples $\geq 85\%$ and no individual result $\leq 75\%$ at 45 minutes). The assay results met the requirements of $\pm 5\%$ of what is stated on the label. Although the dissolution profile of the generic and innovator was not equal through difference and similarity factors calculation, one batch of generics met the dissolution profile standard of the innovator. So, both generic and innovator drugs met the standards of assay and dissolution, even though the dissolution profiles were not equivalent.

KEYWORDS: Assay; dissolution; gefitinib.

INTRODUCTION

Globocan 2020 estimated that lung cancer is the world's second most commonly diagnosed cancer (11.4%) and the leading cause of cancer death, with 1.8 million deaths [1]. Syahrudin et al. found 44.4% population of EGFR mutation among newly diagnosed or treatment-naïve Indonesian lung cancer patients (years 2015–2016) [2]. Gefitinib is a targeted therapy that inhibits the tyrosine kinase activity of the epidermal growth factor receptor by blocking the ATP binding site competitively [3]. As first-line therapy for non-small cell lung cancer with EGFR mutations recommended by the National Comprehensive Cancer Network (NCCN) [4]. Nurhayati et al did research a Cost-Effectiveness Analysis of TKIs in the National Respiratory Center Hospital (2017–2019) and found that gefitinib was the most cost-effective TKI compared to erlotinib and afatinib [5]. Gefitinib started to be accommodated in the National Formulary (Fornas) in 2015 so that it was available in National Health Insurance called Jaminan Kesehatan Nasional (JKN) services with the innovator product being the only product distributed in Indonesia [6]. In the middle of 2021, innovator gefitinib was replaced by a generic product with an 86.67% price decrease (information from the hospital procurement unit). In line with Sarnianto et al research in 2022 the product price that won the e-catalog has been considered too low, however, they have had registration numbers from the Indonesian Food and Drugs Authority (BPOM) and are eligible to participate and win the tender. There for is a challenge to prove whether the generic quality is equal to the innovator product [7].

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Following the regulation of the head of BPOM No 28/2017; one of 3 core activities of the general function of BPOM is post-market supervision of food and drugs through sampling and testing, this research participates to ensure the medicine quality on the market[8]. We were interested in supervising these drugs because the price difference between the generic product and the innovator is quite large and its role as a drug of choice of NSCLC, is high volume, and high cost in spending cancer therapy.

Gefitinib's chemical name was N-(3-chloro-4-xylopropoxy)quinazolin-4-amine with a molecular weight was 446.902363 g/mol, and its molecular formula was $C_{22}H_{24}ClFN_4O_3$ [9]. Gefitinib exhibits high lipophilicity, placing it within the biopharmaceutical classification system (BCS) Class 2. This classification signifies low aqueous solubility but favorable intestinal permeability[10]. Indonesian equivalence test guidelines state that drugs in this class can be subjected to a dissolution test to determine equivalence with the comparison product (innovator)[11]. A drug's pharmacological activity, a fundamental prerequisite for absorption and subsequent clinical response, is intricately tied to the nature of its dissolution behavior. This well-established connection between the in vitro dissolution rate, observed in laboratory settings, and a drug's bioavailability in vivo (within the body) is formalized through In Vitro-In Vivo Correlation (IVIVC). IVIVC frameworks allow researchers to predict a drug's bioavailability based on its dissolution profile measured under controlled in vitro conditions[12].

Generic product as a sample in this research was the first generic and single winner of e-catalog procurement in 2020 and started to be used in therapy in the middle of 2021 until December 2022. Doctors' and pharmacists' negative perception of generic medication has been found by a systematic review of 52 observational studies over 1980 in the world including Asia's countries. This systematic review was held by Colgan et al 2015[13]. Siahaan et al 2017 stated there was still a negative perception of generic product safety in 3 provinces of Indonesia[14]. There this research aimed to know the equivalence of medicine quality between the innovator and the generic, so that the innovator is interchangeable with the generic.

Several analytical methods have been employed to assess the quality and composition of Gefitinib tablets. Sandhya et al. (2013) utilized High-Performance Liquid Chromatography (HPLC) for this purpose, achieving reliable results[9]. This method is not only easy and reliable, but it also offers a robust method for gefitinib analysis. This makes it particularly well-suited for this research to determine the assay and dissolution of gefitinib. Furthermore, the analytical method for Gefitinib Tablets has not yet been incorporated into the official pharmacopeia. By exploring this alternative approach, we hope to contribute valuable insights and potentially pave the way for its future inclusion as a standardized method.

■ MATERIALS AND METHODS

Material

We randomly collected an innovator tablet from the official distributor and sampled 3 batches of generic products from two hospitals i.e., National Respiratory Center Persahabatan Hospital and National Cancer Center Dharmas. The three batches were all generic batches that have been used in Indonesian JKN services for 1.5 years (mid-2021 – December 2022) and we call it generic batch 1, generic batch 2, and generic batch 3. Generic batch 3 was the newest made by the manufacturer. European pharmacopeia reference material for standard analysis, reagents: methanol, monobasic potassium phosphate, and reverse osmosis water. The types of equipment that we used are general laboratory glassware, High-Performance Liquid Chromatography – Ultraviolet (HPLC-UV) Waters® Alliance 2695 with UV Detector at 247 nm, analytical balance, and filter. Dissolution testing used solution tween 80 (5% v/v) in 1000 mL water.

The assay method of the Gefitinib tablet does not yet exist in the pharmacopeias, in Indonesian Pharmacopeia, United States Pharmacopeia, or European Pharmacopeia, so the method refers to previous research by Sandhya et al, 2013[9]. Regarding the development of an analysis method for gefitinib tablet preparations using gefitinib raw materials, then the method was modified for analysis of gefitinib tablet preparations. The method validation process was carried out based on the ICH Topic Q2 (R1) guidelines from the European Medicine Agency (EMA)[15]. The chromatographic conditions of HPLC used were mode liquid chromatography (LC), detector UV 247 nm, C18 column, methanol : buffer (90:10) as mobile phase, flow rate 1 mL/min, and 10-minute run time. The value range of results (sample assay) should meet the requirement of $100 \pm 10\%$ [16]. The dissolution test used the FDA 2010 method with tween 80 (5% v/v) in 1000 mL water, speed 50 RPMs with apparatus II paddle. The dissolution filtrate was taken in minutes 10, 20, 30, 45 and 60. The concentration from each minute point is depicted in a graph as a dissolution profile. The equality of the

dissolution profile was assessed by calculating the unsimilarity factor (F1) and similarity factor (F2). F1 quantifies the relative discrepancy between the reference and test dissolution profiles at each time point, expressed as a percentage difference. Mathematically, F1 is calculated as:

$$\text{Unsimilarity Factor (F1)} = \frac{\sum(R_t - T_t)}{\sum(R_t)} \times 100$$

In this equation, n represents the number of time points, R_t symbolizes the dissolution value of the reference batch at time t , and T_t denotes the dissolution value of the test batch at time t . The similarity factor (F2) provides a quantitative measure of resemblance between the dissolution profiles of the reference and test products. Unlike F1, which emphasizes point-to-point differences, F2 utilizes a logarithmic transformation of the sum of squared errors, encompassing the overall profile similarity[17].

$$\text{Similarity Factor (F2)} = 50 \log \left[\frac{100}{\sqrt{1 + \frac{\sum_{t=1}^{t=n} [R_t - T_t]^2}{n}}} \right]$$

According to the dissolution specification of the innovator brochure, the standard is $\geq 85\%$ with a mean ($n=6$) and no individual result $\leq 75\%$ at 45 minutes[18].

Validation procedure

To ensure the validity of the analytical methodology, a validation process was conducted by the parameters outlined in ICH Q2 (R1)[15]. This process assessed specificity, linearity, limit of detection (LOD), limit of quantitation (LOQ), accuracy, precision, and robustness. Subsequently, the applicability of the validated methodology was confirmed by evaluating the dissolution profiles of innovator and generic gefitinib batches. The procedures of parameter determination are briefly described below.

System suitability test (SST)

Prepare 0.25 mg/mL gefitinib standard solution and transfer it into a vial. To check the SST, it is injected five times from the same vial. It should be produced The relative standard deviation (RSD) NMT 2.0% for the analyte and internal standard.

Specificity

Prepared placebo solution transferred into a vial. Specificity is determined by measuring the interference of the analyte in the placebo solution. The analyte response in the placebo should be no more than 2% compared to the analyte response in the standard at a concentration level of 100%.

Linearity

Linearity is determined by measuring the correlation coefficient (r) of the sample solution at five level concentrations (50, 125, 200, 250, and 300 $\mu\text{g/mL}$) for three replications for each concentration level. The coefficient correlation (r) should be not less than 0.990 ($r \geq 0.990$).

Accuracy and precision

Accuracy is determined by measuring the % recovery of sample solution for three-level concentrations (80, 100, and 120%). Accuracy should be obtained for three replications for each concentration level with % recovery 98 to 102%. In the same procedure way, precision is determined by %CV for three replications for each concentration level which should be no more than 2%.

Robustness (Variability of flow rate)

Prepare sample solution at 100% concentration level only in 6 replications and were transferred into the vial. Inject sample solution for robustness with flow rate of mobile phase at 0.8 mL/minute, 1 mL/minute, and 1.2 mL/minute into the HPLC system. The robustness is determined by measuring the percentage (%CV) for six replications for each flow rate which should be within 2%.

RESULTS

Validation process results

Testing showed the method was specific, with no interference (0%) from inactive ingredients at the chosen wavelength, well below the set limit of 2% compared to a standard Gefitinib solution as proven in Table 1. The

method was also linear across a range of 50 to 300 µg/mL (represented by the equation $y = -121657x + 37512.77$ and a strong correlation coefficient of $r^2 = 0.999$) as described in Table 2.

Table 1. Specificity of the analytical method for dissolution of Gefitinib.

Sample Name	Area Gefitinib	%Interference of Gefitinib
Specificity 1	0	0.00
Specificity 2	0	0.00

Table 2. Linearity of the analytical method for dissolution of Gefitinib.

Slope	Intercept	R ²	R
37512.77	-121657	0.9999	0.9999

The test's precision was evaluated through repeatability. When injecting six replications at 100% dosage (250 mg), the Relative Standard Deviation (RSD) was low, at 0.16%, as the best RSD. This indicates high consistency within a single analysis session. To assess accuracy, Gefitinib standard solution at three levels (200.06, 250.07, and 300.08 µg/mL) was spiked into vessels containing all inactive ingredients (excipients). The recovered amounts were 79.88%, 100.34%, and 119.76% of the spiked quantities, respectively. This indicates good agreement between the measured values and the actual concentrations. The precision of these measurements was also high, with RSD values below 0.82% for all three spiking levels. Details of these results, including the absorbance values, can be found in Table 3.

Table 3. Accuracy of the analytical method for dissolution of Gefitinib. The limit of RSD is < 2%.

Accuracy Sample	Amount (µg/mL)	Mean Amount (µg/mL)	%RSD	%Recovery
80%	199.82	199.76	0.60	79.88
	200.93			
	198.52			
100%	250.81	250.91	0.16	100.34
	251.36			
	250.57			
120%	299.92	299.48	0.81	119.76
	301.65			
	296.88			

The robustness of the analytical method was evaluated by investigating the influence of flow rate variations on the target analyte response. Flow rates were tested at $\pm 20\%$ of the nominal value (e.g. if the nominal flow rate was 1 mL/min, rates of 0.8 mL/min, and 1.2 mL/min were tested). No significant changes in %CV for six replications for each flow rate were observed for the analyte of interest, indicating that the method is robust to these typical variations in flow rate. This ensures consistent and reliable results even under minor operational fluctuations. While formal validation procedures may not always require robustness testing, incorporating it into the protocol offers valuable insights. This knowledge ensures the method's effectiveness under real-world conditions, where minor variations may occur.

Table 4. Flow rate robustness of the analytical method for dissolution of Gefitinib The limit of RSD < 2%.

Rate (mL/min)	Mean Amount (µg/mL)	SD	%RSD
0.8	247.01	3.03	1.23
1.0	247.94	1.94	0.78
1.2	248.48	2.38	0.96

Assay

Each group innovator and generic consists of 2 batches (duplo) for assay and through the same testing steps. All samples meet the requirements in the assay. The results of concentrations were in the range of $100 \pm 5\%$. The assay percentage of the innovator was 100.07% and 3 batches of the generic were 99.29%, 101.09%, and 104.41%.

Table 5. The result of Innovator and Generic Gefitinib assay. The limit is $\pm 5\%$ (18)

Code	Tablet Average Weight (mg)	Sample	Area Gefitinib	Assay (%)	Average (%)
Innovator	515.90	1	9036542	99.15	100.70
		2	9204068	100.99	
Generic Batch 1	516.45	1	9073452	99.55	99.29
		2	9025451	99.03	
Generic Batch 2	517.18	1	9135193	100.23	101.09
		2	9292041	101.95	
Generic Batch 3	519.93	1	9437044	103.54	104.41
		2	9594462	105.27	

Dissolution test

According to the dissolution profile of innovator gefitinib informed in the BPOM-approved brochure, with a mean ($n=6$) is $\geq 85\%$ and no individual result $\leq 75\%$ at 45 minutes [18], we used this as the standard of dissolution of gefitinib. Generic batch 3 meets this standard.

The calculation of difference (unsimilarity) and similarity factors from 3 batches generic were out of the standard range. It means that the two groups have no similarity in dissolution profile. Generic batch 3 is the nearest profile to the innovator standard. From Table 4 we can see that both profiles reached above 90% within 60 minutes of dissolution. From Table 6 and Figure 1, we can see the results of F1 (unsimilarity factor) and F2 (similarity factor) are out of the limits.

Table 6. Result of assay at points of generic and innovator product batch 1.

No.	Sampling time (minutes)	Average of Dissolution		(R - T)	(R - T) ²
		Test (T)	Reference (R)		
0	0	0.00	0.00	0.00	0.00
1	10	20.66	36.09	15.43	237.95
2	20	43.96	78.03	34.07	1160.75
3	30	65.99	89.08	23.09	533.17
4	45	83.44	93.51	10.07	101.40
5	60	90.71	95.65	4.94	24.42
Total (Σ)		304.76	392.35	87.60	2057.69
Limit				Result	
F1		0 - 15		22,33	
F2		50 - 100		34,61	

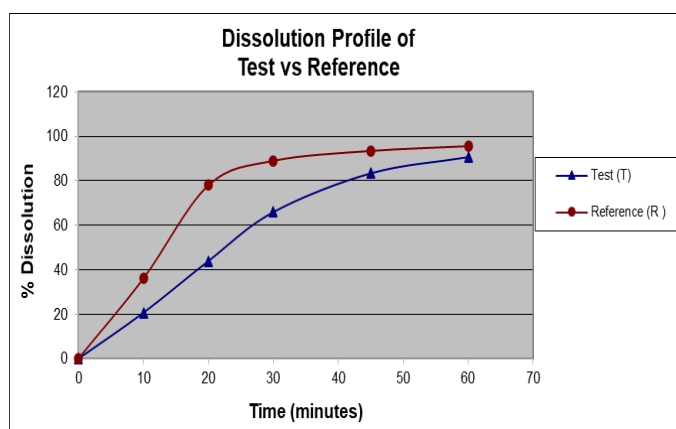
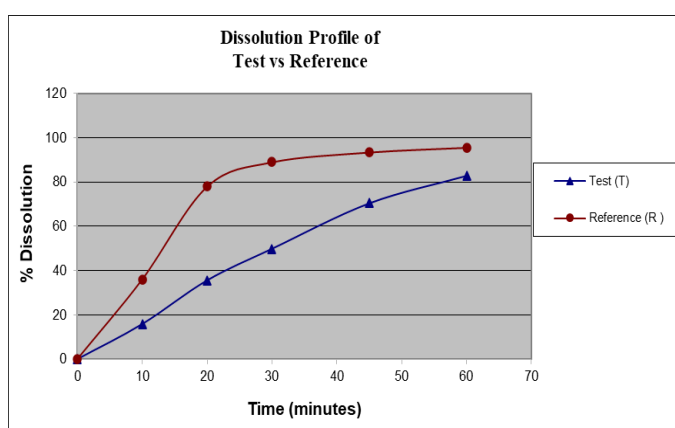
**Figure 1.** The dissolution profile generic batch 1 vs innovator.

Table 7. Result of assay at points of generic and innovator product batch 2.

No.	Sampling time (minutes)	Average of Dissolution		(R - T)	(R - T) ²
		Test (T)	Reference (R)		
0	0	0.00	0.00	0.00	0.00
1	10	15.87	36.09	20.22	408.78
2	20	35.62	78.03	42.40	1797.98
3	30	49.90	89.08	39.18	1534.86
4	45	70.45	93.51	23.06	531.83
5	60	82.87	95.65	12.78	163.23
Total (Σ)		304.76	254.72	392.35	137.64
Limit				Result	
F1				0 - 15	
F2				50 - 100	
				22.33	
				34.61	

**Figure 2.** The dissolution profile generic batch 2 vs innovator

From Table 7 and Figure 2, we can see the results of F1 (unsimilarity factor) and F2 (similarity factor) are out of the limits.

Table 8. Result of assay at points of generic and innovator product batch 3.

No.	Sampling time (minutes)	Average of Dissolution		(R - T)	(R - T) ²
		Test (T)	Reference (R)		
0	0	0.00	0.00	0.00	0.00
1	10	28.10	36.09	7.99	408.78
2	20	55.09	78.03	22.94	1797.98
3	30	75.79	89.08	13.29	1534.86
4	45	88.45	93.51	5.06	531.83
5	60	93.02	95.65	2.63	163.23
Total (Σ)		304.76	247.43	296.70	49.27
Limit				Result	
F1				0 - 15	
F2				50 - 100	
				16.61	
				42.53	

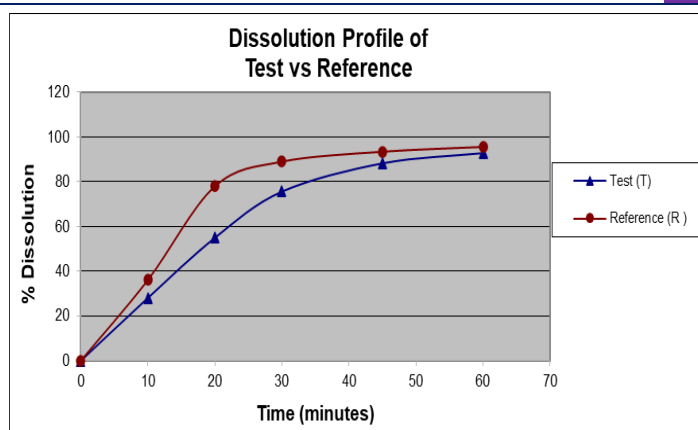


Figure 3. The dissolution profile generic batch 3 vs innovator

From Table 8 and Figure 3, we can also see the results of F1 (unsimilarity factor) and F2 (similarity factor) are out of the limits.

Table 9. Result of assay at point of generic batch 3 samples (n=6).

Tablet	Sample weight (mg)	% Dissolution					
		0	10	20	30	45	60
1	511.67	0.00	36.44	67.08	79.59	90.96	94.26
2	516.57	0.00	31.27	61.15	80.99	89.58	92.14
3	518.71	0.00	29.30	55.84	77.60	87.05	93.11
4	529.48	0.00	28.99	57.30	80.55	90.96	94.54
5	528.51	0.00	20.43	40.82	65.36	85.77	91.78
6	517.03	0.00	22.17	48.35	70.64	86.40	92.32
Average		0.00	28.10	55.09	75.79	88.45	93.02
SD		0.00	5.93	9.33	6.36	2.33	1.15
%RSD		0.00	21.09	16.93	8.40	2.64	1.24

Generic batch 3 has the nearest dissolution profile to reference (innovator product). From Table 9, we can see the average of 6 samples $\geq 85\%$, and all samples are $>75\%$ in 45 minutes. There are no individual results $\leq 75\%$, that meet the standard of innovator specification in the BPOM registration profile[18].

DISCUSSION

In vitro testing or quality control of drugs is a set of experiments to be done during production (in process) and postproduction by regulatory agencies and researchers[19]. Dissolution, a time-dependent process describing the formation of a uniform solid-in-liquid mixture, is a crucial property of pharmaceutical dosage forms. It involves the breakdown of the solid drug into its constituent particles (ions, atoms, or molecules) followed by their solvation. Beyond its role as a quality control test, dissolution is increasingly recognized as a potential predictor of bioavailability. In some cases, dissolution data may even hold promise for replacing clinical bioequivalence studies[20]. BPOM stated that assay and dissolution tests are important parameters to guarantee post-market medicine quality[21]. Another bioequivalence test is in vivo which is evaluated from the human body that has consumed the drugs and measures drug concentration in blood, but this method needs more difficult requirements because involves humans as a sample.

In Indonesia, ensuring the quality of medicines is paramount, particularly for those included in the JKN program, which provides national health insurance. The BPOM plays a vital role in this endeavor. BPOM implements a robust post-market surveillance program to continuously monitor the quality, safety, and efficacy of medicines after they have been approved for public use[22]. This approach complements the rigorous pre-market evaluations conducted before medications enter the market. Through this study, we aim

to contribute valuable data that aligns with BPOM's post-market surveillance efforts and further strengthens quality control measures for Gefitinib tablets used within the JKN program.

Gefitinib is a poorly water-soluble drug, which shows poor absorption/bioavailability after oral administration (BCS class 2). Therefore gefitinib should be tested by dissolution test to find out whether the drug is equivalence to the reference, generic product to the innovator. A similar study that has been carried out is a comparative dissolution of innovator and generic atorvastatin by Aini et al., 2015[23]. Atorvastatin is in the same class as BCS as gefitinib. They compared the dissolution profile of branded generic and the generic to the innovator. Dissolution testing and assay also were done by Putri et al., 2016 on branded and generic ranitidine[24].

The dissolution profile of Gefitinib has not been available in pharmacopeia (Indonesian, United States, or European), so we adapted from Sandhya's research in 2013 and the FDA method dissolution method then we did a validation process in the laboratory[9]. From the result of validation, we can see that they met the standards, which leads to the use of this method as a dissolution method of gefitinib. Several analytical methods have been explored for the quantification of Gefitinib. The existing research landscape for Gefitinib analysis remains somewhat limited. Notably, the method employed by Navya et al. (2017), though validated, focused on quantifying Gefitinib within a polymeric nanoformulation, differing from the commercially available tablet form[25].

In this study, we collected samples from all batches that have been used in JKN services for 1,5 years (mid-2021 – Des 2022). We found 3 batches and tested them. The batch 3 was the newest made by manufacturers. From the assay results, we see that innovator and generic products meet the quality standard of drug concentration. In the dissolution test, we found that batch 3 of the generic meets the dissolution standard of the innovator product informed in a brochure (average of 6 samples $\geq 85\%$ and no individual result $\leq 75\%$ at 45 minutes)[18]. Even though the dissolution profile of generic and innovator were not equal through difference and similarity factors calculation.

Dissimilarities in the dissolution profiles of generic and innovator tablets can have significant ramifications for public health. The efficacy of drug substances is highly dependent on their bioavailability, which is influenced by the rate and extent of drug release from the tablet[26]. In public health systems, where cost-effectiveness is a major concern, ensuring generic products possess comparable dissolution profiles to the innovator is crucial. Furthermore, such disparities can erode patient confidence in generic medications, potentially hindering treatment adherence and overall health outcomes. However, the dissolution profile of the innovator gefitinib product, which was announced as a standard specification in the BPOM-approved brochure [18], has been fulfilled in the dissolution test results of the generic product. This made a judgment that the generic product met the standards, so innovator and generic are interchangeable.

▪ CONCLUSION

This research showed that the generic and innovator products met the requirement for assay, whereas in the range of $100 \pm 5\%$ of 250 mg gefitinib. Even though they were not equal in dissolution profiles through difference and similarity factors, but generic batch 3 met the dissolution standard of innovator gefitinib (average of 6 samples $\geq 85\%$ and no individual result $\leq 75\%$ at 45 minutes). So, the innovator product can be interchanged with the generic.

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