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COMPARATIVE DISSOLUTION BEHAVIOUR OF TEN MARKETED CHLORAMPHENICOL CAPSULES IN INDONESIA

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ABSTRACT: Background: Chloramphenicol capsules are found in several brands with different prices in the market. This study aimed to obtain *in-vitro* biopharmaceutics quality data from the generic and branded name products. **Methods:** Ten products were selected, consisted of 3 generics (A, B and C) and 7 branded names (D, E, F, G, H, I and J); F was chosen as an innovator. The dissolution test was performed by using the basket method in medium 0.01 N HCl pH 1.28 ± 0.05; the analysis was done using spectrophotometer UV-Visible at 277.6 nm. The dissolution profiles were analyzed using a kinetic equation and similarity factor. AnX-ray diffraction analysis was done to confirm the results. **Results:** There were no significant differences in the amount dissolves in 20 minutes between the innovator and other products ($p>0.05$). Products A, C, H, I and J were similar with the innovator; the f_2 values were 54.82; 50.74; 66.16; 91.34 and 51.35% respectively. Other products (B, D, E, and G) were not similar. The diffractogram showed similar pattern indicating an amorphous form with different peak intensity. **Conclusion:** All products were by the requirements of the 5th Indonesian Pharmacopoeia; however, there were differences in dissolution profiles which supports the reason for different efficacy and prices.

INTRODUCTION: Chloramphenicol is available as capsules containing chloramphenicol palmitate to obtain more pleasant taste. This antibiotic is a BCS (Biopharmaceutics Classification System) Class III drug with high solubility but low permeability [1]. It exists in three polymorphic forms: A, B and C. Polymorph B less stable but dissolves better than form A; polymorph C is unstable. Form A biologically inactive, on the other hand, form B biologically active.

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Differences in the polymorphic form shown significant contribution to variability in the dissolution profile among dosage form [2]. There are ten brands of Chloramphenicol capsules marketed with different prices in Indonesia. The branded names are more expensive than the generic capsules. It is our interest to ensure whether higher price correlates with better quality and vice versa. Further, the results might support the production and the use of generic products in the community.

MATERIALS AND METHODS:

Materials: Prednisone calibrator tablets, prednisone reference standard, and chloramphenicol reference standard were obtained from the Indonesian Food and Drug Controlling Agency. Ten products of chloramphenicol palmitate capsules 250 mg were purchased, consisted of 3

generic products (A, B and C) and 7 branded name products (D, E, F, G, H, I and J). Hydrochloric acid (HCl, Merck), pH 7.4 phosphate buffer and distilled water were used as dissolution media.

Methods: Pharmaceutical quality assessment of Chloramphenicol Capsules

- **a.** General physical appearance [3].
- **b.** Weight uniformity (Libror AEG-80 Digital Balance) [3].
- **c.** Disintegration time (Pharma Test Disintegration tester 3) [3].
- **d.** Drug content by Spectrophotometer UV-Visible (Shimadzu 1800) [3].

Comparative Dissolution Test of Chloramphenicol: [3]

Suitability test of the Dissolution Apparatus: Dissolution tester (Hanson Research SR6) was calibrated by measuring the dissolution of 6 prednisone calibrator tablets in 900 mL 0.05 M phosphate buffer solution pH 7.4 ± 0.05 (Metrohm Seven Easy pH meter) at 37 ºC as a medium. The paddle was set at 50 rpm. Samples (5 mL) were withdrawn at minute 30th and diluted to 25 mL with the medium. The same suitability test procedure was also conducted by using the basket method.

Validation of the Analytical Method [3]: Quantitative analysis was done by using Spectrophotometer UV-Vis at the maximum wavelength of 277.6 nm. The method was validated by measuring absorbances of standard chloramphenicol solutions in HCl 0.01 N at concentration 0.0055, 0.0083, 0.0110, 0.0166 and 0.0221 mg/ml respectively.

Dissolution Test [3]: Dissolution test of 6 capsules from each brand was performed by using the USP dissolution apparatus I (basket system, stirring rate of 100 rpm) with a medium of 900 mL 0.01 N HCl solution pH 1.28 ± 0.05 at 37º ± 0.5 ºC. Samples (2 mL) were taken at 1, 5, 10, 20, 40, and 60 min respectively, diluted to 25 mL with the medium. The concentration of chloramphenicol dissolved was determined by the validated spectro-photometric method at the maximum wavelength of 277.6 nm.

Dissolution Data Analysis:

Model Dependent Method: The dissolution profile of each brand was plotted and data were then analyzed according to Langenbucher equation, a modification of the Weibull model of drug release [4]:

$$[\log[-\ln(1- m)] = b\log(t - Ti) - \log a] \quad \text{.....(1)}$$

Where:
m= fraction of drug dissolved at time t
a = scale parameter
t = time
Ti = lag time
b = curve parameter

The percentage of chloramphenicol dissolved from each brand at 20 min (Q20) was analyzed by using one-way ANOVA.

Model-Independent Method: The dissolution profiles of each product were compared to the profile of innovator by using similarity factor (f2) using the equation below 5:

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

Where:
Rt = cumulative percentage of reference (innovator) drug dissolves at sampling time.
Tt = cumulative percentage of tested product dissolves at sampling time.
'n = number of capsules tested per product = 6

The dissolution profile of tested products is claimed to have similarity or equivalent with that of the reference if $f_2 > 50\%$.

X-Ray diffraction (XRD) Analysis 6: XRD analysis was performed by using X-ray diffractometer (X'pert PRO, PAN analytical) equipped with copper Kα radiation (40 kV, 20 mA). The scanning was done from 5º to 50º 2θ for chloramphenicol powder in capsules.

RESULTS AND DISCUSSION: System suitability test using calibrator tablets indicated that the dissolution apparatus met the USP dissolution apparatus suitability criteria where 0.5 - 31.3% (apparatus 1) and 0.3 - 10.2% (apparatus 2) prednisone was released in 30 min [7]. Validation of the analytical method showed a linear correlation between absorbances and concentrations with

regression equation of: y = 0.0013 x + 0.0345 (r = 0.9997).

Evaluation of the physicochemical and pharmaceutical properties of chloramphenicol capsules showed that all brands fulfilled the requirements of the 5th Indonesia Pharmacopeia **Table 1**. The assay of drug content showed that all the products were by the requirements listed in the Pharmacopeia quality levels of 90% - 120% [3]. The amount of chloramphenicol dissolved at minute 30th (Q30) stated in the 5th Indonesia Pharmacopeia is more than 85%, this requirement is also met. In this study, the amount dissolved in 20 min (Q20) well discriminates the drug released from all products tested. Statistical analysis by one-way ANOVA showed no significant difference in Q20 between an innovator (product F) with products A, B, C, D, E, G, H, I and J ($p>0.05$). Product F was chosen as the innovator in this study because it was highly used clinically. These data indicate that all chloramphenicol capsules marketed in Indonesia met the official standard set by the government.

TABLE 1: PHYSICOCHEMICAL AND PHARMACEUTICAL PROPERTIES OF CHLORAMPHENICOL CAPSULES

Physicochemical properties	Products									
	A	B	C	D	E	F	G	H	I	J
Dosage form	capsule	capsule	capsule	capsule	capsule	Capsule	capsule	capsule	capsule	capsule
Color	White-green	White-green	Green	Yellow-blue	Yellow	White-green	Yellow-green	Yellow-green	Blue-black	Yellow-red
Odor	Odorless	Odorless	Odorless	Odorless	Odorless	Odorless	Odorless	Odorless	Odorless	Odorless
Weight ± SD (mg)	316.14 ±1.58	298.92 ±0.60	300.95 ±0.95	277.12 ±2.47	283.89 ±0.84	302.07 ±0.94	331.22 ±1.20	276.04 ±1.62	341.48 ±4.15	309.56 ±3.80
Disintegration time ± SD (min)	7.00 ±1.11	7.05 ±1.17	7.76 ±0.38	6.76 ±0.35	6.75 ±0.75	6.59 ±0.58	6.38 ±0.81	5.46 ±0.81	6.19 ±0.82	7.75 ±0.69
Drug content (%)	101.58	100.24	97.13	99.01	101.55	103.85	100.63	101.14	96.74	101.2
Q_{20} ± SD	90.7 ±4.51	86.07 ±4.42	90.65 ±4.74	82.94 ±8.35	80.88 ±4.39	99.96 ±2.47	80.20 ±1.98	99.67 ±0.42	98.49 ±3.78	101.75 ±7:21

Drug dissolution rate is well correlated with the *in-vivo* performance of a dosage form; therefore dissolution test is compulsory in the quality control of drug products [8]. Dissolution rate is affected by the physicochemical properties of the active ingredient including particle size, solubility, the crystalline form and also the manufacturing techniques [8]. The use of different raw materials from various suppliers may contribute to a different in solubility and hence dissolution time among brands [2]. Analysis of dissolution profile using the kinetic model and similarity factor has been done to compare the biopharmaceutics quality of all chloramphenicol capsules tested.

The dissolution profile of all brands of chloramphenicol capsules **Fig. 1A** and **1B** were obtained by plotting the percentage of drug dissolved versus time. The profiles showed that all products are completely dissolved in 60 min. Four products (F, H, I and J) were rapidly dissolved (>60%) in 5 min, this correlated well with a rapid onset of therapy which is necessary for the treatment of infection.

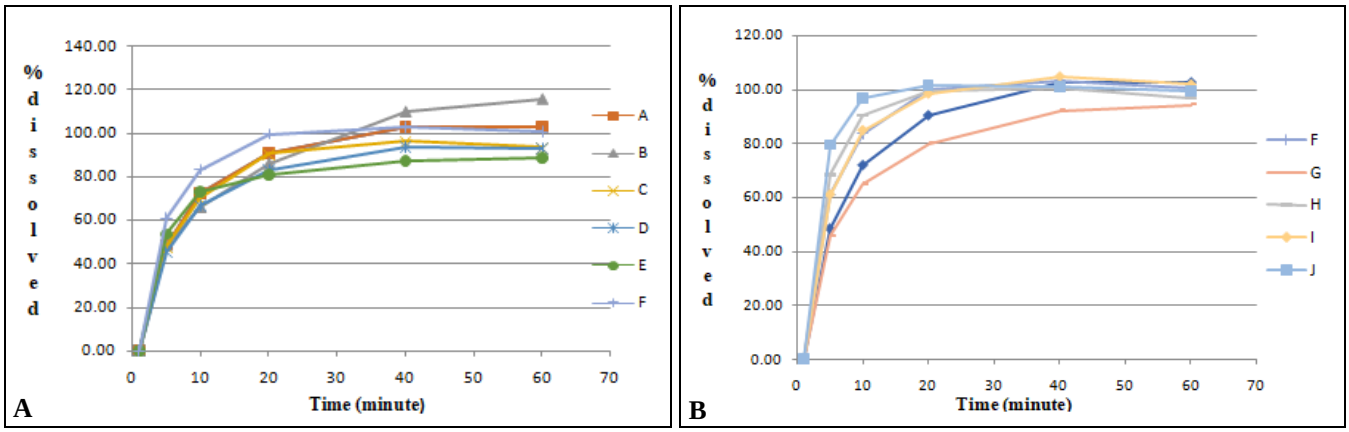

FIG. 1: DISSOLUTION PROFILES OF CHLORAMPHENICOL CAPSULES MARKETED IN INDONESIA (A, B, AND C ARE GENERIC PRODUCTS; AND D, E, F, G, H, I AND J ARE BRAND NAMES PRODUCTS)

The dissolution data were then analyzed according to Langenbucher equation to determine the kinetic profile. The dissolution profiles of products A, B, C, D, E, F, G, H and I showed a good agreement with this equation (r>0.9500) except product J **Fig. 2**. The slope of the trendline indicates that products A-I follow a similar mechanism of drug release, a passive diffusion [4]. The mechanism and rate of drug dissolved are a function of the type of excipients and the capsule shell. Higher dissolution rates provide a higher amount of drug available to be absorbed in the digestive tract [8].

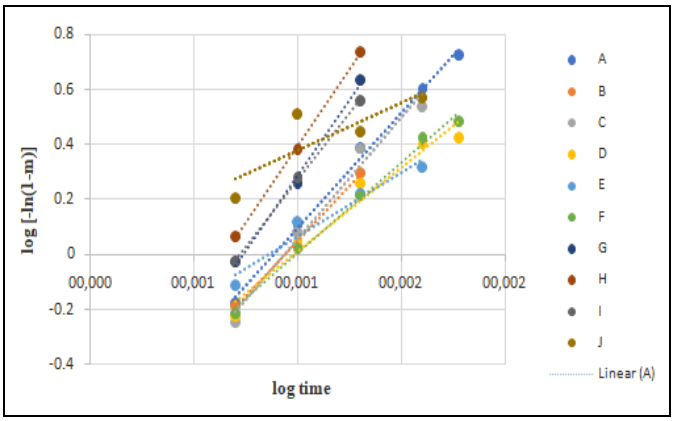

FIG. 2: LANGENBUCHER PLOT OF THE DISSOLUTION OF CHLORAMPHENICOL CAPSULES MARKETED IN INDONESIA IN 0.01 N HCl MEDIUM

Comparative dissolution study is also conducted by calculation of the similarity factor between the innovator and each product. The f_2 value greater than 50% indicates similarity or equivalence in the dissolution profile of one product with the comparator (Innovator) [5]. The f_2 values **Table 2** showed that products A, C, H, I and J are similar with their innovator, however products B, D, E, and G are not similar.

Product F is the most commonly prescribed by the physicians for typhoid therapy therefore chosen as a benchmark for other products. Results in **Table 2** confirm that although all products meet the minimum official standards, the pharmaceutical quality is different which causes differences in therapeutic effectiveness and of course the price.

TABLE 2: SIMILARITY FACTOR (f_2) VALUES OF CHLORAMPHENICOL CAPSULES A, B, C, D, E, G, H, I AND J IN COMPARISON TO F

No	Products	F2	Similarity
1	A (generic)	54.82	Yes
2	B (generic)	45.20	No
3	C (generic)	50.74	Yes
4	D (brand name)	44.67	No
5	E (brand name)	45.24	No
6	F (brand name)	100	Innovator
7	G (brand name)	43.14	No
8	H (brand name)	66.16	Yes
9	I (brand name)	91.34	Yes
10	J (brand name)	51,35	Yes

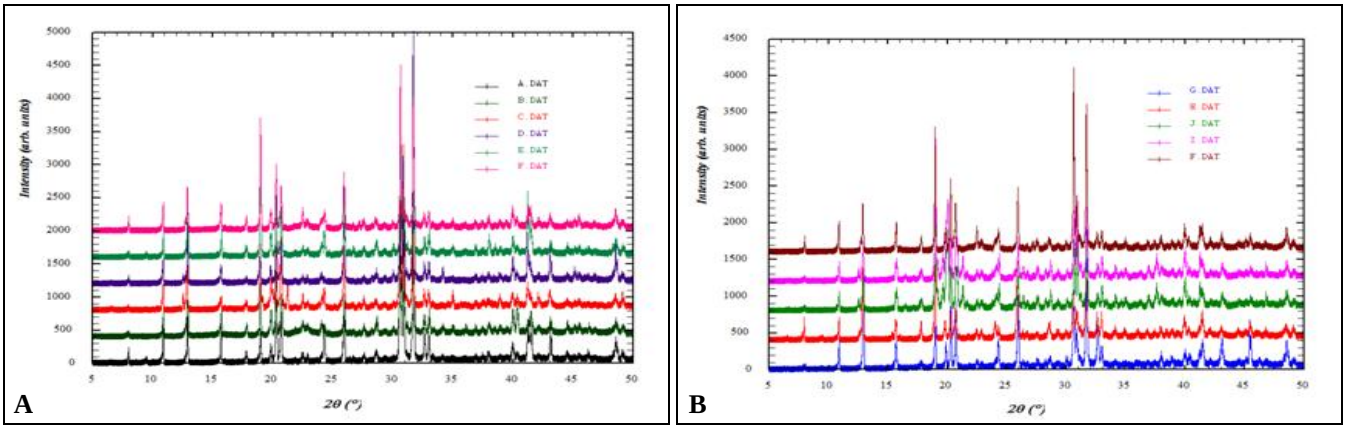

FIG. 3: THE XRD PATTERNS OF CHLORAMPHENICOL CAPSULES A, B, C, D, AND E IN COMPARISON TO F (3.1) AND CAPSULES G, H, I, AND J IN COMPARISON TO F (3.2)

A difference in the pharmaceutical quality of dosage forms may is due to the variabilities in particle morphology of chloramphenicol raw materials. Chloramphenicol has 3 types of polymorph which differ in solubility and consequently dissolution time among brands [2]. Furthermore, the type of excipients used in the formula also determined the physicochemical and pharmaceutical properties of capsules. To evaluate the effect of particle morphology on the dissolution of the capsules, an XRD analysis was conducted. The diffractograms **Fig. 3A** and **3B** showed a similar pattern of the amorphous form used in all products; however, varies in crystallinity degree

indicated by peak intensity of the interference. A decrease in crystallinity index indicates the use of a smaller particle size of chloramphenicol and other excipients used in capsules [2]. These data support that all products are using the same polymorph form but different particle size distribution of the basic form of chloramphenicol raw materials.

The United States Food and Drug Administration stated that the drug products are pharmaceutically equivalent if the product contains the same ingredients and the same strength, dosage form and route of administration. Product is considered therapeutically equivalent if the drug is pharmaceutically equivalent and can be expected to provide the same therapeutic effect when administered to patients under the conditions stated in etiquette [1].

CONCLUSION AND SUMMARY: In summary, all brands met the requirements of the 5th Indonesia Pharmacopeia especially in dissolution time (Q_{30}); however, there were differences in dissolution profiles which supports the reason for different efficacy and prices. The bioavailability of chloramphenicol is permeability rate limited, thus the higher dissolution rate of chloramphenicol is necessary to provide a rapid availability of molecular form to be absorbed to exert a rapid onset of therapy. These results also showed that price differences correlate with differences in pharmaceutical quality and also probably the bioavailability of the drug. This study also supports the use of generic chloramphenicol capsules because they have met an official quality standard. It is recommended that for polymorphism drugs, a procedure to identify the type of the polymorph exists in the formulation should be employed, to assure the bioequivalence of the marketed products in patients.

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CONFLICT OF INTEREST: The authors declared no conflict of interest.

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