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Pharmacokinetic and bioequivalence studies of generic clarithromycin tablets in healthy male volunteers

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Clarithromycin is a broad spectrum macrolide antibacterial agent which is effective against the major pathogens responsible for respiratory tract infections [1–5]. After oral administration, clarithromycin is rapidly absorbed. The maximal plasma concentrations (C_{max}) of clarithromycin following a single oral dose is achieved within 3 h [6, 7]. The maximal plasma concentrations of clarithromycin after single doses of 500 mg administration was 2.12 ± 0.83 mg/l. The time to peak concentration was 1–3 h [8].

The objective of this study was to assess the average bioequivalence of two formulations of 500 mg clarithromycin tablets: Claron® manufactured by Siam Bheasach, Thailand (test formulation) and reference formulation in healthy Thai male volunteers. The clinical protocol was approved by the Ethics Committee of the Ministry of Public Health, Thailand.

Clarithromycin was well tolerated. No volunteer was withdrawn and no serious adverse event was found during the study.

From the dissolution study, it appeared that% dissolution of the test and reference preparation at 60 min, different factor (f_1) and similarity factor (f_2) were $94.2 \pm 1.3\%$ ($n = 12$) and $93.0 \pm 1.2\%$ ($n = 12$), 4.2 and 56.2 respectively. Average concentration-time courses of clarithromycin after single 500 mg clarithromycin tablet administrations of both preparations in 24 health Thai male subjects are shown in the Fig. 1. Maximal clarithromycin levels of the test and reference were observed after 2.5 ± 0.8 h and 2.2 ± 0.9 h respectively. The average peak concentration (C_{max}), area under the curve from 0–24 h. (AUC_{0-24}) and area under the concentration-time curve ($AUC_{0-\infty}$) of test and reference

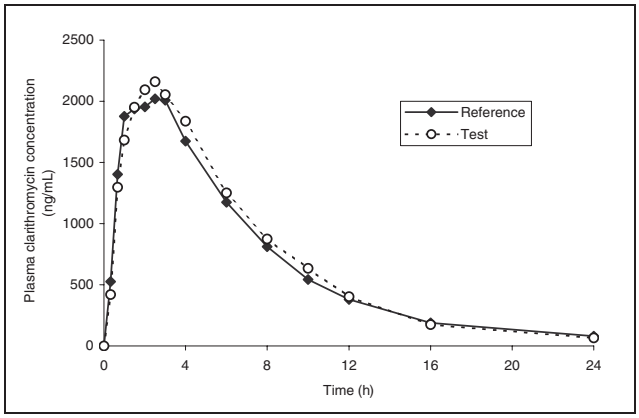

Fig.: Plasma concentration-time curve of clarithromycin after 500-mg single dose administration of reference and test formulations in 24 healthy Thai male volunteers.

were 2429 ± 1079 vs. 2322 ± 1096 ng/ml, 16527 ± 7770 vs. 15699 ± 6206 ng · h/ml and 16935 ± 8019 vs. 16293 ± 6286 ng · h/ml, respectively. The mean half-lives ($t_{1/2}$) were 3.5 ± 0.9 h for the test and 3.9 ± 1.1 h for the reference. The relative bioavailability was 1.05.

The test/reference ratio for C_{max} and the 90% confidence interval were 1.01 and 93.1–124.6%. The test/reference ratio for $AUC_{0-\infty}$ and the 90% confidence interval were 1.00 and 88.9–119.2% (Table 1).

In summary, regarding both C_{max} and $AUC_{0-\infty}$ of clarithromycin, the bioequivalence of both formulations of 500-mg clarithromycin tablets was concluded. Therefore, these two preparations can be used interchangeably in clinical practice.

Experimental

1. Study design and clinical protocol

In a randomized, balanced, single dose, fasting, two-period, two-sequence, crossover study with a 1-week washout period, 24 healthy Thai male volunteers were enrolled with the age and body mass index of 20.6 ± 0.8 years and 20.5 ± 1.6, respectively. All healthy volunteers provided written informed consent before enrollment. The volunteers were non-smoking, non-alcoholic and free from cardiac, hepatic, renal, gastrointestinal, and hematological diseases.

In the evening before the experiment, the subjects were admitted to the Bioequivalence Test Center. After overnight fasting, they received a tablet containing 500 mg of clarithromycin along with water. Standard meals were provided, and no other food was permitted during the study. Liquid consumption was allowed *ad libitum* but xanthine containing and acidic beverages were prohibited.

2. Drug analysis

Blood samples were collected into a lithium-heparinized containing tube before dosing and at 0.33, 0.67, 1, 1.5, 2, 2.5, 3, 4, 5, 6, 8, 12, 16 and 24 h after-clarithromycin administration. The samples were centrifuged, separated and then plasma samples were kept at $-80\,^{\circ}C$ until assayed.

The samples were assayed by a validated HPLC method with electrochemical detection, using roxithromycin as an internal standard [7, 8]. In brief, the 0.5 ml of plasma sample was extracted by liquid-liquid extraction. The HPLC systems consisted of Constametric 3200 (Thermo Separa-

Table: Arithmetic and geometric mean and 90% confidence intervals (90% C.I.) of C_{max} and $AUC_{0-\infty}$ (log transformed) of clarithromycin after 500-mg single dose administrations of reference and test formulations in 24 healthy Thai male volunteers

	Arithmetic mean ± SD		Geometric mean ± SD		SEM[a]	90% C.I.	Acceptable range
	Test	Reference	Test	Reference	(Test/Reference)		
C_{max}	2429 ± 1079	2322 ± 1096	7.72 ± 0.38	7.65 ± 0.48	0.085	93.1–124.6	80–125
$AUC_{0-\infty}$	16935 ± 8019	16293 ± 6286	9.66 ± 0.38	9.63 ± 0.37	0.085	88.9–119.2	80–125

[a] $SEM = \sqrt{EMS \cdot (1/N_A + 1/N_B)}$.

tion Products, San Jose, USA), series 200 autosampler (Perkin Elmer, Wellesley, USA) and Coulochem II electrochemical detector (Environmental Sciences Assoc., Chelmsford, USA) with +850 mV (guard cell), +500 mV (E1) and +780 mV (E2). The Waters Spherisorb C-8 analytical column (Waters Corp., Milford, USA), 5 µ, 150 × 4.6 mm was used. The mobile phase was composed of acetonitrile : methanol : acetate buffer (50 : 10 : 40) with pH 7.5. The flow rate was 1.3 ml/min. The calibration curve of clarithromycin ranged from 90 to 3600 ng/ml. The limit of quantitation was 18 ng/ml. The % recovery, % accuracy and within-run precision (% C.V.) of clarithromycin in spiked plasma samples at the concentrations of 90, 360 and 1800 ng/ml were 99.6, 84.5, and 89.1%, 95.7, 101.3 and 100.0% and 7.2, 3.7 and 8.1% respectively. The % recovery and % C.V. of the internal standard in spiked plasma samples were 90.7% and 8.8% respectively.

3. Pharmacokinetic and statistical analysis

A non-compartmental pharmacokinetic method was employed to determine the pharmacokinetic parameters of clarithromycin. The time to peak plasma concentration (T_{max}) and the peak concentration (C_{max}) were obtained directly from the plasma clarithromycin concentrations. WinNonlin Standard (version 3.0) was used to determine area under the concentration-time curve ($AUC_{0-\infty}$) and half-life ($t_{1/2}$). $AUC_{0-\infty}$ was calculated by linear trapezoidal method.

An analysis of variance (ANOVA) was performed on the pharmacokinetic parameters C_{max} and $AUC_{0-\infty}$, using general linear models (GLM) procedures, in which sources of variation were sequence, subjects within sequence, period, and preparation. Then the 90% confidence intervals of the test/reference ratios for C_{max} and $AUC_{0-\infty}$ (log transformed) were determined. Bioequivalence between two formulations could be concluded when the 90% confidence intervals for these pharmacokinetic parameters of two products are found within the acceptable range of 80–125%.

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Meloxicam complexation with β-cyclodextrin: influence on the anti-inflammatory and ulcerogenic activity

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Non-steroidal anti-inflammatory drugs (NSAIDs) are widely used to provide effective anti-inflammatory and analgesic therapy to patients with arthritis. However, they are associated with a high incidence of gastrointestinal (GI) side effects, which can reduce patient compliance and discourage physicians from prescribing them [1]. Therefore there is a need for a delivery system for NSAIDs with improved GI tolerability, while retaining efficacy.

Cyclodextrins are widely used in the pharmaceutical field owing to their high aqueous solubility and ability to stabilize drug molecules. They are known for their ability to encapsulate a wide variety of drugs into their hydrophobic cavity without the formation of any covalent bonds [2–6].

Meloxicam is a preferential COX-2 inhibitor with strong anti-inflammatory activity. It is practically insoluble in water and has a longer onset of action. Its prolonged use is associated with incidence of side effects like GI perforations, ulcerations and bleeding. Therefore the aim of the present study was to investigate the effect of inclusion of meloxicam with β-cyclodextrin (β-CD) upon anti-inflammatory activity and GI mucosal toxicity.

The β-CD complex of meloxicam was prepared by the freeze-drying (FD) method [7] and showed a faster onset of anti-inflammatory activity than the pure drug, freeze dried similarly (pH 5.0 ± 0.1), indicating a maximum inhibition of oedema. A peak inhibition of 80.0% was obtained at 2 h in the group of mice, which was treated with meloxicam-β-CD (FD) solution (pH 4.9 ± 0.1), but for

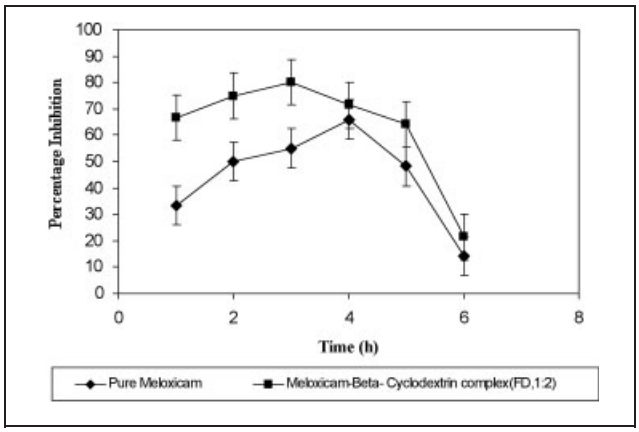

Fig.: Anti-inflammatory studies of meloxicam and meloxicam/β-CD complex by rat hind paw odema method (mean ± SD; n = 4)