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BIOEQUIVALENCE OF TWO BRANDS OF GLIPIZIDE TABLETS

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A Thesis Submitted in Partial Fulfillment of the Requirements
for the Degree of Master of Science in Pharmacy in Pharmacy

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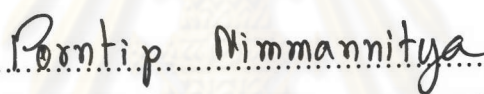
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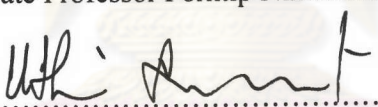
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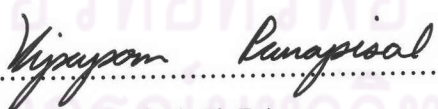

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ดำเนินการศึกษาชีวสมมูลของยาเม็ดไกลิพิไซด์ขนาด 5 มิลลิกรัม 2 ผลิตภัณฑ์ โดยเบื้องต้นทดสอบคุณภาพยาตามมาตรฐานที่กำหนดในเภสัชตำรับสหรัฐอเมริกาฉบับที่ 27 และเปรียบเทียบเส้นโค้งของผลิตภัณฑ์ยาที่ผลิตในประเทศไทยกับผลิตภัณฑ์ยาดัชนีแบบด้วยวิธีแบบจำลองอิสระพบว่ายาทั้ง 2 ผลิตภัณฑ์มีการบ่งชี้, ความสม่ำเสมอของตัวยาคำคัญในผลิตภัณฑ์, ร้อยละของยาที่ระบุนิว์บนฉลาก และการละลายยาได้มาตรฐานตามเกณฑ์ที่กำหนด และเส้นโค้งการละลายของผลิตภัณฑ์ยาทั้งสองมีลักษณะเหมือนกัน การเปรียบเทียบชีวปริมาณออกฤทธิ์ของยาเม็ดไกลิพิไซด์ทั้ง 2 ผลิตภัณฑ์ ใช้อาสาสมัครชายไทย สุขภาพดี 12 คน ตามแผนการทดลองแบบสุ่มข้ามสลับซ้ำอาสาสมัครแต่ละคนได้รับยาสามัญที่ผลิตในประเทศไทย และยาดัชนีแบบซ้ำ 2 ครั้ง โดยการรับประทานครั้งละ 1 เม็ด และเว้นระยะห่างการให้ยา 1 สัปดาห์ในแต่ละครั้ง เก็บตัวอย่างเลือดที่เวลาต่าง ๆ นาน 12 ชั่วโมงหลังการรับประทานยา ตรวจวัดความเข้มข้นของไกลิพิไซด์ในพลาสมาด้วยเอชพีแอลซี กำหนดค่าพารามิเตอร์ทางเภสัชจลนศาสตร์ที่เกี่ยวข้องจากกราฟความเข้มข้นของไกลิพิไซด์ในพลาสมา-เวลาและเปรียบเทียบโดยใช้การวิเคราะห์ความแปรปรวน ผลปรากฏว่าค่าพื้นที่ใต้เส้นโค้งระหว่างความเข้มข้นของยาในพลาสมา-เวลา ความเข้มข้นของยาสูงสุดในพลาสมาที่แปลงข้อมูลอยู่ในรูปลอการิทึมและค่าอื่นๆแสดงตัวแปรเกี่ยวกับสูตรตำรับของยาทั้ง 2 ผลิตภัณฑ์ไม่แตกต่างกันทางสถิติที่ระดับความเชื่อมั่นร้อยละ 95 ค่าร้อยละ 90 ของช่วงความเชื่อมั่นของสัดส่วนของพื้นที่ใต้เส้นโค้งระหว่างความเข้มข้นของยาในพลาสมา กับเวลา และความเข้มข้นของยาสูงสุดในพลาสมาในเทอมของค่าเฉลี่ยลอการิทึมของยาสามัญที่ผลิตในประเทศไทย เทียบกับผลิตภัณฑ์ยาดัชนีแบบอยู่ภายในช่วงร้อยละ 80-125 ค่าเฉลี่ยของเวลาที่ความเข้มข้นของยาสูงสุดในพลาสมามีความแตกต่างกันร้อยละ 20.45 ดังนั้นจึงสรุปได้ว่าผลิตภัณฑ์ยาเม็ดไกลิพิไซด์ทั้งสองตำรับมีชีวสมมูลกันทั้งในเชิงอัตราเร็วและปริมาณยาที่ถูกดูดซึมเข้าสู่ร่างกาย ค่าพารามิเตอร์ทางเภสัชจลนศาสตร์ที่ได้รับจากการศึกษานี้มีความสอดคล้องและใกล้เคียงกับค่าเดียวกันที่ได้รายงานไว้แล้ว

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ลายมือชื่อนิสิต..... *พรสิริ จิตรถเวช*

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PONSIREE JITHAVECH: BIOEQUIVALENCE OF TWO BRANDS OF
GLIPIZIDE TABLETS. THESIS ADVISOR: ASSOC. PROF. UTHAI
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The present study was carried out to evaluate bioequivalence between two brands of glipizide tablets. *In vitro* tests revealed that both brands met the specified criteria of the United States Pharmacopoeia 27 specifications according to identification, uniformity of dosage units, assay and dissolution test, indicating pharmaceutical equivalence. The dissolution profiles of a generic product and an innovator's product were similar based on model independent method. Comparative bioavailability of the two brands was conducted in 12 healthy Thai male volunteers using randomized replicated crossover design with 1 week washout period between treatments. After an orally single dose administration, serial blood samples were collected for 12 hours and plasma concentrations of glipizide were determined by high performance liquid chromatography. Relevant pharmacokinetic parameters of the two brands were calculated from plasma glipizide concentration-time profiles and compared using analysis of variance. Results showed that there were no statistically significant differences ($p > 0.05$) in area under the plasma drug concentration-time curve (AUC) and peak plasma drug concentration (C_{max}) based on log-transformed data, including other pharmacokinetic parameters with respect to formulation effect of both products. The 90% confidence intervals for the ratios of mean log-transformed data of a generic product relative to an innovator's product of AUC_{0-12} , $AUC_{0-\infty}$ and C_{max} were within 80-125%. Difference of t_{max} means was 20.45%. This indicated that the two brands tested were bioequivalent regarding to the rate and extent of absorption. Pharmacokinetic parameters found in this experiment agreed and closed to those previously reported.

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LIST OF ABBREVIATIONS

ALT	=	alanine aminotransferase
ANDA	=	abbreviated new drug application
ANOVA	=	analysis of variance
AST	=	aspartate aminotransferase
AUC	=	area under the plasma concentration-time curve
AUC ₀₋₁₂	=	area under the plasma concentration time curve from zero to 12 hours
AUC _{0-∞}	=	area under the plasma concentration time curve from zero to infinite time
BMI	=	body mass index
°C	=	degree Celcius
CI	=	confidence interval
CL	=	clearance
C _{max}	=	peak plasma concentration
C.V.	=	coefficient of variation
d.f.	=	degree of freedom
Exp	=	expiration
f ₁	=	difference factor
f ₂	=	similarity factor
F	=	fraction of dose to be absorbed
FDA	=	Food and Drug Administration
GI	=	gastrointestinal
hr	=	hour
HPLC	=	high performance liquid chromatography
HQC	=	high quality control concentration
IBE	=	individual bioequivalence
IV	=	intravenous
kg	=	kilogram
K _e	=	elimination rate constant

L	=	liter
%L.A.	=	percent labeled amount
LLE	=	liquid-liquid extraction
LLOQ	=	lower limit of quantification
Ln	=	natural logarithms
LQC	=	low quality control concentration
mg	=	milligram
min	=	minute
mL	=	milliliter
M	=	molar
Mfg	=	manufacturing
MQC	=	medium quality control concentration
MRT	=	mean residence time
MS	=	mean square
MSE	=	mean square error
ng	=	nanogram
nm	=	nanometer
N	=	normality
NDA	=	new drug application
NS	=	not significant difference at $p > 0.05$
PBE	=	population bioequivalence
QC	=	quality control concentration
r^2	=	coefficient of determination
rpm	=	revolution per minute
Ref.	=	reference
RS	=	reference standard
R.S.D.	=	relative standard deviation
S	=	significant difference at $p < 0.05$
S.D.	=	standard deviation
S.E.	=	standard error
SPE	=	solid phase extraction
SS	=	sum of squares

Subj. x Form. (Seq.)	=	subject x formulation (sequence)
$t_{1/2}$	=	half-life
t_{max}	=	time to peak plasma concentration
μg	=	microgram
μL	=	microliter
μm	=	micrometer
USP	=	United States Pharmacopeia
UV	=	ultraviolet
v/v	=	volume by volume
V_d	=	apparent volume of distribution
WS	=	working standard



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