

การตั้งตำรับ ความคงตัวและชีวสมมูลของยาพ่นจมูกแซลมอนแคลซิโทนิน



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จุฬาลงกรณ์มหาวิทยาลัย

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FORMULATION, STABILITY AND BIOEQUIVALENCE OF
SALMON CALCITONIN NASAL SPRAYS

Miss Bordeesuda Suiwongsa

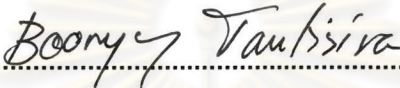


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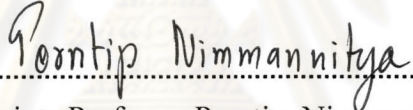
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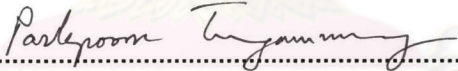
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นางสาวคิสุดา ชูยวงศ์ษา: การตั้งตำรับ ความคงตัวและชีวสมมูลของยาพ่นจมูกแคลสมอน
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แคลซิโทนิน(แคลสมอน) เป็นเป็ปโตได์ที่ใช้ในการรักษาภาวะกระดูกพรุน และโรคความ
ผิดปกติอื่นของกระดูก ในปัจจุบันยาที่มีใช้ในประเทศไทยอยู่ในรูปแบบยาฉีดและยาพ่นจมูก ซึ่งทั้ง
สองรูปแบบยังต้องนำเข้าจากต่างประเทศส่งผลให้ยามีราคาแพงและมีการใช้ในวงจำกัด
วัตถุประสงค์หลักของการศึกษาค้นคว้าครั้งนี้คือต้องการที่จะพัฒนาตำรับยาแคลสมอนแคลซิโทนินในรูปแบบ
ยาพ่นจมูกที่มีความคงตัวดี มีชีวประสิทธิผลและมีราคาถูกกว่าเดิม ยาพ่นจมูกแคลสมอนแคลซิ
โทนินถูกเตรียมขึ้นเป็นสองความแรงได้แก่ 100 และ 200 ยูนิต ตำรับละสองรุ่นการผลิต ยาพ่นจมูก
ที่เตรียมได้อยู่ในรูปสารละลายใส มีความเป็นกรดต่ำและโทนิซิตีที่เหมาะสม บรรจุใส่ขวดพ่นเฉพาะ
สามารถให้ละอองแต่ละครั้งพ่นเท่ากับ 0.09 มล. ทำการศึกษาความคงตัวในสภาวะเก็บปกติ (4 องศา
เซลเซียส) เป็นเวลา 12 เดือนและสภาวะเร่งอุณหภูมิ (30 องศาเซลเซียส) เป็นเวลา 4 เดือน โดยเก็บ
ตัวอย่างมาตรวจตามช่วงเวลาที่กำหนดไว้ เพื่อหาปริมาณตัวยาคัญ และนอกเหนือไปจากนั้นได้ทำ
การหาปริมาณสารละลายตัว(แคลซิโทนิน ซี) พร้อมกับปริมาณของเป็ปโตได์ที่มีโครงสร้างใกล้เคียงกัน
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ออส โมลาลิตี ความสม่ำเสมอของการให้สเปรย์ และความเป็นกรดต่ำของยาพ่นจมูก ตลอด
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การวิเคราะห์โดยใช้เทคนิคทางเรดิโออิมมิวโนโลยี จากการวิเคราะห์ข้อมูลทางสถิติพบว่า ค่าความ
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กับเวลาของผลิตภัณฑ์ทั้งสองตัวอย่างไม่มีความแตกต่างอย่างมีนัยสำคัญ ($p>0.05$) ค่าร้อยละ 90 ของช่วง
ความเชื่อมั่นของสัดส่วนของแต่ละพารามิเตอร์ทางเภสัชจลนศาสตร์เทียบกับยาต้นแบบอยู่ในช่วง
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และมีความเท่าเทียมกันในทางเภสัชกรรม

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BORDEESUDA SUIWONGSA: FORMULATION, STABILITY AND BIOEQUIVALENCE OF SALMON CALCITONIN NASAL SPRAYS.

THESIS ADVISOR: ASSOC. PROF. PARKPOOM TENGAMNUAY, Ph. D.
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Salmon calcitonin (CT) is a peptide used in the treatment of osteoporosis and other bone-related disorders. It is currently available in Thailand as an injection and a nasal spray solution, both of which are imported resulting in a high cost of medication and limited usage. The main objective of this study was to develop salmon CT nasal spray preparations that could provide acceptable stability and bioavailability at a more economical cost. Two strengths (100 and 200 IU per actuation) of salmon CT nasal sprays were prepared (two batches each). The formulation was an isotonic solution of synthetic salmon CT with appropriate preservative, buffer and tonicity adjuster. A special spray pump was used that could provide an accurate and reproducible spray volume of 0.09 ml per actuation. The stability studies consisted of real-time testing at 4 °C (recommended storage condition) for 12 months and at 30 °C (accelerated condition) for 4 months. Samples were taken periodically to determine for salmon CT content as well as its degradation product (calcitonin C) and related peptide (N-acetyl-cys¹-calcitonin) by HPLC. The percent labeled amount of all four batches was within 90.0 – 115.0 % ranges. The prepared nasal sprays also complied with the tests for calcitonin C and related peptide as well as the clarity, pH, osmolarity, uniformity of mass and sterility tests under both storage conditions. The reproducibility of the pump spray performance was also confirmed based on the results from the leak test, droplet size distribution and spray pattern evaluation. The *in vivo* bioavailability of the test product (200 IU strength) relative to the innovator product was further evaluated in 12 healthy male volunteers. Each subject received a total single dose of 400 IU salmon CT in a two-way crossover study. The plasma concentrations of salmon CT were determined by radioimmunoassay. There were no statistically significant differences in the corresponding pharmacokinetic parameters (AUC and C_{max}) between the two products ($p > 0.05$, ANOVA). The 90% confidence intervals for the ratio of the two parameters (test to innovator) based on the log-transformed data were within the 80.0 – 125.0% bioequivalence range. Thus, it can be concluded that the prepared salmon CT nasal spray solutions were both pharmaceutically equivalent and bioequivalent to the innovator product.

Department Pharmacy
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Student's signature.....*Bordesuda Suwongsa*

Advisor's signature.....*Parkpoom Tengamnuay*

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จุฬาลงกรณ์มหาวิทยาลัย

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LIST OF ABBREVIATIONS

%	=	Percent
% L.A.	=	percent labeled amount
°C	=	degree Celsius
µg	=	Microgram
µL	=	Microliter
µm	=	Micrometer
¹²⁵ I	=	Iodine 125
Å	=	Angstrom
ANOVA	=	analysis of variance
AUC	=	area under the plasma concentration – time
B	=	bound radio-labeled antigen
B ₀	=	unbound radio-labeled antigen
BMI	=	body mass index
BP	=	British Pharmacopoeia
CDER	=	Center for Drug Evaluation and Research
C.I.	=	confidence interval
C.V.	=	coefficient of variation
cm	=	Centimeter
C _{max}	=	peak plasma concentration
CPM	=	Counts per minute
CT	=	Calcitonin
D ₁₀	=	10% of the droplet diameters are smaller than the indicated value
D ₅₀	=	50% of the droplet diameters are smaller than the indicated value
D ₉₀	=	90% of the droplet diameters are smaller than the indicated value
Da	=	Dalton
EDQM	=	European Directorate for the Quality Medicine
EP	=	European Pharmacopoeia
EPCRS	=	European Pharmacopoeia Control Reference

FDA	=	Food and drug administration
HPLC	=	high performance liquid chromatography
hr	=	Hour
I.U.	=	international unit
k_e	=	elimination rate constant
kg	=	Kilogram
L	=	Liter
LLOQ	=	lower limit of quantitation
\ln	=	natural logarithms
m	=	Meter
M	=	Molar
Mfg.	=	Manufacturing
m^2	=	square meter
mg	=	Milligram
min	=	Minute
mL	=	Milliter
mm	=	Milliliter
mOsmol	=	Milliosmol
MSE	=	mean square error
MW	=	molecular weight
N	=	Normality
nm	=	Nanometer
No.	=	Number
NSB	=	non - specific binding
pg	=	Pictogram
q.s.	=	quantum sufficiat
r^2	=	coefficient of determination
RIA	=	Radioimmunoassay
rpm	=	revolution per minute
S.D.	=	standard deviation
S.E.	=	standard error
$t_{1/2}$	=	half life
t_{max}	=	time to peak plasma concentration

USP	=	United States Pharmacopoeia
UV	=	Ultraviolet
v/v	=	volume by volume
w/v	=	weight by volume
w/w	=	weight by weight
WHO	=	World Health Organization



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