

การพัฒนาตำรับและการประเมินผลในกระต่าย  
ของผลิตภัณฑ์ยาสตาเวอไดนิคออกฤทธิ์นานในรูปแบบเพลเลต

นางสาวทิพย์สุดา คารวมิตร

วิทยานิพนธ์นี้เป็นส่วนหนึ่งของการศึกษาตามหลักสูตรปริญญาเภสัชศาสตรมหาบัณฑิต  
สาขาวิชาเภสัชอุตสาหกรรม ภาควิชาเภสัชอุตสาหกรรม  
คณะเภสัชศาสตร์ จุฬาลงกรณ์มหาวิทยาลัย  
ปีการศึกษา 2549  
ลิขสิทธิ์ของจุฬาลงกรณ์มหาวิทยาลัย

FORMULATION DEVELOPMENT AND IN VIVO EVALUATION IN RABBITS  
OF STAVUDINE EXTENDED-RELEASE PELLETS

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A Thesis Submitted in Partial Fulfillment of the Requirements  
for the Degree of Master of Sciences in Pharmacy Program in Industrial Pharmacy

Department of Manufacturing Pharmacy

Faculty of Pharmaceutical Sciences

Chulalongkorn University

Academic Year 2006

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492254

Thesis Title                    FORMULATION DEVELOPMENT AND IN VIVO EVALUATION IN  
RABBITS OF STAVUDINE EXTENDED-RELEASE PELLETS  
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Field of Study                  Industrial Pharmacy  
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ทิพย์สุดา คารวมิตร : การพัฒนาตำรับและการประเมินผลในกระต่ายของผลิตภัณฑ์ยาสตาเวอดีนชนิดออกฤทธิ์นานในรูปแบบเพลเลท. (FORMULATION DEVELOPMENT AND IN VIVO EVALUATION IN RABBITS OF STAVUDINE EXTENDED-RELEASE PELLETS) อ. ที่ปรึกษา : รศ.ดร. พจณี กุลวานิช, อ.ที่ปรึกษาร่วม : ดร.สุชาติ วัฒนศิริชัยกุล. 181 หน้า.

สตาเวอดีนเพลเลทเตรียมขึ้นโดยกระบวนการเอ็กทราซันสเฟียไรในเซชัน โดยศึกษาถึงอิทธิพลของตัวแปรในการผลิต คือ ความเร็วในการหมุนของสเฟียไรโรเตอร์ และเวลาที่ใช้ในกระบวนการสเฟียไรในเซชัน ที่มีผลต่อคุณสมบัติทางกายภาพของเพลเลท ความกลมของเพลเลทจะเพิ่มขึ้นเมื่อเพิ่มความเร็วในการหมุนของสเฟียไรโรเตอร์ระหว่างกระบวนการเตรียมมวลเปียก เมื่อเวลาที่ใช้ในกระบวนการสเฟียไรในเซชันเพิ่มขึ้น จะทำให้ได้เพลเลทที่มีความกลม พื้นผิวเรียบ และขนาดอนุภาคเฉลี่ยของเพลเลทเพิ่มขึ้น เพลเลทที่ใช้ Avicel<sup>®</sup> PH101 ที่ความเร็วในการหมุนของสเฟียไรโรเตอร์สูง จะมีอนุภาคทรงกลม การกระจายขนาดแคบ มีคุณสมบัติการไหลดี นอกจากนี้ยังมี angle of repose และความกร่อนต่ำ อีกทั้งไม่มีความแตกต่างระหว่าง bulk density และ tapped density สภาวะที่เหมาะสมในการเตรียมสตาเวอดีนเพลเลท คือ ตำรับที่ประกอบด้วย ยาสตาเวอดีน 40%, Avicel<sup>®</sup> PH101 60%, น้ำ 65% โดยใช้ความเร็วในการหมุนของสเฟียไรโรเตอร์ 860 รอบต่อนาที เป็นเวลา 10 นาที สตาเวอดีนเพลเลทชนิดควบคุมการปลดปล่อยเตรียมโดยเคลือบเพลเลทแกนด้วยสัดส่วนและปริมาณต่างๆ กันของสารเคลือบ Surelease<sup>®</sup> และ HPMC E15 LV สัดส่วนของ Surelease<sup>®</sup> และ HPMC E15 LV มีผลอย่างมากต่อการปลดปล่อยตัวยา โดยการปลดปล่อยตัวยาจะเพิ่มขึ้นเมื่อปริมาณของ HPMC E15 LV ในสารละลายที่ใช้เคลือบเพิ่มขึ้น ทั้งนี้เนื่องมาจากการรั่วของฟิล์มส่วนที่ละลายน้ำได้ (HPMC E15 LV) ระหว่างการละลาย ซึ่งจะทิ้งรูพรุนสำหรับการปลดปล่อยตัวยา ส่วนผสมของ Surelease<sup>®</sup> และ HPMC E15 LV 95 : 5 ที่ระดับการเคลือบเพิ่มขึ้น 20% แสดงลักษณะการปลดปล่อยตัวยาเป็นไปตามต้องการ กลไกการปลดปล่อยตัวยาจากเพลเลทเคลือบเป็นแบบปฏิกิริยาอันดับศูนย์ วิธีวิเคราะห์ในหลอดทดลองได้ถูกตรวจยืนยัน ซึ่งแสดงความเที่ยงตรง แม่นยำและจำเพาะ ทั้งยา Zerit<sup>®</sup> IR และสตาเวอดีนเพลเลทมีความคงตัวอย่างน้อย 6 เดือนเมื่อเก็บผลิตภัณฑ์ไว้ที่ 30 องศาเซลเซียส ความชื้นสัมพัทธ์ 65 % และที่ 40 องศาเซลเซียส ความชื้นสัมพัทธ์ 75 %

การดำเนินการเปรียบเทียบค่าเภสัชจลนศาสตร์ของยาสตาเวอดีนเพลเลทและยา Zerit<sup>®</sup> IR กระทำในกระต่ายพันธุ์นิวซีแลนด์สีขาวจำนวน 12 ตัว แต่ละตัวได้รับยาสตาเวอดีนเพลเลท 100 มก. และ Zerit<sup>®</sup> IR 50 มก. ครั้งเดียวตามแบบการทดลองสุ่มข้ามสลับชนิดสองทาง โดยเว้นระยะเวลา 2 สัปดาห์ระหว่างการบริหารยา ตัวอย่างเลือดถูกเก็บที่ช่วงเวลาเฉพาะต่างๆ แยกพลาสมาและวิเคราะห์ความเข้มข้นของยาสตาเวอดีนในพลาสมาโดยวิธีไฮเพอฟอร์แมนซ์ลิควิดโครมาโตกราฟีที่ได้พัฒนาและตรวจยืนยัน ในการศึกษา ค่าเฉลี่ยของพื้นที่ใต้กราฟระหว่างความเข้มข้นของยาในพลาสมา กับเวลา ตั้งแต่ 0 ชม. ถึงเวลาสุดท้ายที่วัดระดับยาในพลาสมาได้ สำหรับยาสตาเวอดีนเพลเลท และยา Zerit<sup>®</sup> IR คือ  $3,214.09 \pm 364.42$  และ  $1,504.79 \pm 222.58$  นก.ชม./มล. ตามลำดับ, ค่าเฉลี่ยของพื้นที่ใต้กราฟระหว่างความเข้มข้นของยาในพลาสมา กับเวลา ตั้งแต่ 0 ชม. ถึงระยะอนันต์ สำหรับยาสตาเวอดีนเพลเลทและยา Zerit<sup>®</sup> IR คือ  $3,585.96 \pm 397.82$  และ  $1,606.21 \pm 237.46$  นก.ชม./มล. ตามลำดับ, ค่าความเข้มข้นสูงสุดของยาในพลาสมาสำหรับยาสตาเวอดีนเพลเลทและยา Zerit<sup>®</sup> IR คือ  $598.83 \pm 61.94$  และ  $1168.03 \pm 74.38$  นก.มล. ตามลำดับ, ค่าเวลาที่ให้ความเข้มข้นสูงสุดของยาในพลาสมาสำหรับยาสตาเวอดีนเพลเลทและยา Zerit<sup>®</sup> IR คือ  $3.29 \pm 0.17$  และ  $0.63 \pm 0.12$  ชม. , ค่าเปอร์เซ็นต์ชีวประสิทธิผลสัมพัทธ์ สำหรับยาสตาเวอดีนเพลเลท คือ  $112.44 \pm 8.92\%$  สรุปได้ว่ายาสตาเวอดีนเพลเลทสามารถดูดซึมได้อย่างสมบูรณ์ โดยมีปริมาณยาที่ถูกดูดซึมแปรผันตามขนาดยาที่เป็นสองเท่าของ Zerit<sup>®</sup> IR อย่างไรก็ตาม อัตราเร็วในการดูดซึมของยาสตาเวอดีนเพลเลทช้ากว่า Zerit<sup>®</sup> IR และระดับยาสตาเวอดีนเพลเลทสามารถอยู่ในร่างกายได้นานกว่า ดังนั้น ยาสตาเวอดีนเพลเลทที่เตรียมขึ้นในการทดลองนี้สามารถเป็นผลิตภัณฑ์ควบคุมการปลดปล่อยตัวยาได้

ภาควิชา.....เภสัชอุตสาหกรรม..... ลายมือชื่อนิสิต..... *Nil Nil*  
 สาขาวิชา.....เภสัชอุตสาหกรรม..... ลายมือชื่ออาจารย์ที่ปรึกษา..... *[Signature]*  
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# # 4676564933 : MAJOR INDUSTRIAL PHARMACY

KEY WORD: STAVUDINE/PELLET/EXTRUSION-SPHERONIZATION

TIPSUDA KARAWAMITR : FORMULATION DEVELOPMENT AND IN VIVO EVALUATION IN RABBITS OF STAVUDINE EXTENDED-RELEASE PELLETS. THESIS ADVISOR : ASSOC.PROF.POJ KULVANICH, Ph.D., THESIS COADVISOR : SUCHAT WATNASIRICHAIKUL Ph.D., 181 pp.

The stavudine pellets were prepared by extrusion and spheronization process. The influence of processing variables, including the spheronizer speed and the spheronization time on physical properties of the pellets, were studied. The sphericity of pellets were increased with increasing spheronizer speed during wet mass process. When spheronization time was increased, sphericity, smooth surface and mean particle size of pellets were increased. Pellets using Avicel<sup>®</sup> PH101 as a diluent at high spheronizer speed showed sphere shape, narrow size distribution and good flow characteristic. The pellets also have a low angle of repose, a low percent friability, and no difference between bulk density and tapped density. The suitable condition for preparing stavudine pellet consisted of 40 %w/w of stavudine, 60 %w/w of Avicel<sup>®</sup> PH101, %65w/w of water and spheronizer speed of 860 rpm with spheronization time at 10 min. The stavudine controlled released pellets were prepared by coating core pellets with Surelease<sup>®</sup> containing HPMC E15 LV at different proportions of coating load. The Surelease<sup>®</sup> : HPMC E15 LV ratio had a major role in the release of drug. The release of the drug increased as the amount of HPMC E15 LV in coating solution was increased. This was thought to be due to the leakage of the soluble part of the film (HPMC E15 LV) during dissolution, which left pores for drug release. The combination of Surelease<sup>®</sup> and HPMC E15 LV of 95 : 5 at 20% coating level provided the drug release profile as requirement. The mechanism of drug release from coated pellets followed zero-order kinetic. The in vitro analytical method was validated and showed linearity, precision, accuracy and specificity. Both Zerit<sup>®</sup> IR and stavudine pellet were stable at least 6 months when products were stored at 30 °C, 65 %RH and at 40 °C, 75 %RH.

The pharmacokinetic comparison of stavudine pellet and Zerit<sup>®</sup> IR was conducted in 12 White New Zealand rabbits. Each subject received a single dose of 100 mg stavudine pellet and 50 mg Zerit<sup>®</sup> IR in a randomized two way crossover design with 2 weeks washout period between dosing. Blood sample were collected at specified time intervals. Plasma was separated and analysed for stavudine concentrations using a developed and validated HPLC method. In this study, The AUC<sub>last</sub> values of stavudine pellet and Zerit<sup>®</sup> IR were 3,214.09 ± 364.42 and 1,504.79 ± 222.58 ng.hr/ml, respectively. The AUC<sub>0,∞</sub> values were 33,585.96 ± 397.82 and 1,606.21 ± 237.46 ng.hr/ml for stavudine pellet and Zerit<sup>®</sup> IR, respectively. The C<sub>max</sub> values values of stavudine pellet and Zerit<sup>®</sup> IR were 598.83 ± 61.94 and 1,168.03 ± 74.38 ng/ml, respectively. The T<sub>max</sub> values of stavudine pellet and Zerit<sup>®</sup> IR were 3.29 ± 0.17 and 0.63 ± 0.12, respectively. Percentage relative bioavailability of stavudine pellet was 112.44 ± 8.92%. It was concluded that stavudine pellet can be completely absorbed and the extent of drug absorption depends on dose given. However, drug absorption rate of stavudine pellet was slower than that of Zerit<sup>®</sup> IR and drug from stavudine pellet can be maintained in plasma longer than Zerit<sup>®</sup> IR. Stavudine pellets which were prepared in this study can be an extend-release product.

Department.....Manufacturing Pharmacy....Student's signature.....*Tipsuda Karawamitr*  
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## ACKNOWLEDGEMENTS

I would like to express my sincere thanks and gratitude to my thesis advisor, Associate Professor Poj Kulvanij, Ph.D. for his helpful advice, guidance, attention, encouragement and understanding. His kindness and helpfulness are also really appreciated.

My special grateful thanks are dedicated to Suchat Watnasirichaikul, Ph.D. my thesis co-advisor who advised, encouraged me and also supported all facilities throughout the study. My thanks are also extended to Associate Professor Uthai Suvanakoot, Ph.D. who spent his valuable time to advice me about the validation method and pharmacokinetic evaluation.

I wish to thank the Research and Development Institute of the Government Pharmaceutical Organization for supporting funds and supplying the costly ingredient such as stavudine and zidovudine in this study.

I also would like to acknowledge all members of my thesis committee for their valuable comments on my thesis.

The special appreciation is expressed to Chulalongkorn University for supporting the grant partially to fulfill this study. A special thankfulness is also given to my friends and the staffs in the Department of Manufacturing Pharmacy for their assistance and great encouragement.

Finally, I would like to express my thanks to all of those whose name have not been mentioned and have helped me to accomplish this thesis.

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## LIST OF ABBREVIATIONS

$^{\circ}\text{C}$	degree celsius (centigrade)
cm	centimeter (s)
d4T	stavudine
EC	ethylcellulose
e.g.	exempli gratia, for example
ER	extended release
et al.	et alii, and others
g	gram (s)
HCl	hydrochloric acid
HPMC	hydroxypropylmethylcellulose
hr	hour (s)
i.e.	id est, that is
IR	immediate release
kg	kilogram (s)
mg	milligram (s)
min	minute (s)
ml	milliliter (s)
mm	millimeter (s)
$\text{mm}^2$	square millimeter (s)
ng	nanogram (s)
N	normal
No	number
pH	the negative logarithm of hydrogen ion concentration
q.s.	quantum satis
$r^2$	coefficient of determination
rpm	revolution per minute
S.D.	standard deviation

SEM	Scanning Electron Microscope
UV	ultraviolet
w/v	weight by volume
w/w	weight by weight
$\mu\text{g}$	microgram (s)
$\mu\text{l}$	microlitre (s)
$\mu\text{m}$	micrometre (s), micron (s)
%	percentage
$^{\circ}$	degree