

การศึกษาคุณลักษณะของ เอ็น-(2-โพรพิลเพนทาโนอิล) ยูเรีย ในสภาวะของแข็ง

นางสาวพัชรินทร์ ศิริอรุณรัตน์



วิทยานิพนธ์นี้เป็นส่วนหนึ่งของการศึกษาตามหลักสูตรปริญญาโทศึกษาศาสตร์มหาบัณฑิต

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SOLID STATE CHARACTERIZATION OF N (2-PROPYLPENTANOYL) UREA

Miss Pasharin Siriaroonrat

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for the Degree of Master of Sciences in Pharmacy

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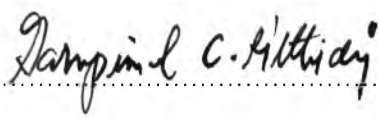
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Thesis Advisor Narueporn Sutanthavibul, Ph.D.  
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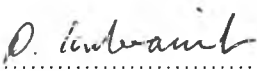
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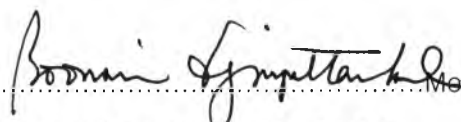
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พัชรินทร์ ศิริอรุณรัตน์ : การศึกษาคุณลักษณะของ เอ็น-(2-โพรพิลเพนทาโนอิล) ยูเรีย ในสภาวะของแข็ง. (SOLID STATE CHARACTERIZATION OF N (2-PROPYLPENTANOYL) UREA) อ. ที่ปรึกษา : อ. ดร. นฤพร สุทัศน์วิบูลย์, อ. ที่ปรึกษาร่วม : ผศ.ดร. ชำนาญ ภัทรพานิช, 105 หน้า. ISBN 974-03-0038-3

การศึกษาคุณสมบัติทางเคมีในสภาวะของแข็งของ เอ็น-(2-โพรพิลเพนทาโนอิล) ยูเรีย (VPU) ซึ่งเป็นสารสังเคราะห์ใหม่ที่มีฤทธิ์ต้านอาการชัก ประกอบด้วย การศึกษารูปแบบของ VPU ในสภาวะของแข็ง ความคงตัวในสภาวะของแข็งของ VPU และ ความสามารถในการละลายของ VPU

การศึกษารูปแบบของ VPU ในสภาวะของแข็ง โดยการนำ VPU มาตกผลึกใหม่ในตัวทำละลายต่างๆ การตกผลึกจากการระเหย การทำให้ VPU หลอมเหลวกลับเป็นของแข็งทันที และ การทำให้เปลี่ยนรูปโดยการใช้ความร้อน จากนั้น นำสารที่ได้มาทดสอบเอกลักษณ์ทางเคมีด้วยวิธี thin layer chromatography (TLC) และ fourier transform infrared spectroscopy (FTIR) และทดสอบรูปแบบของแข็งของสารโดยวิธี x-ray powder diffraction (XRPD) จากนั้นเลือกบางตัวอย่างมาทดสอบโดยวิธี differential scanning calorimetry (DSC) thermogravimetry (TGA) และ scanning electron microscopy (SEM) ไม่พบความแตกต่างของ รูปแบบ XRPD ระหว่างสารที่นำมาทดสอบ ยกเว้น ตัวอย่างที่ได้จากการตกผลึกใน hexane และ heptane โดยการระเหยตัวทำละลายออกอย่างรวดเร็ว (วิธีที่ 1) และไม่พบความแตกต่างของรูปแบบ DSC และ TGA ในตัวอย่างที่นำมาทดสอบ ไม่พบหลักฐานที่สนับสนุนว่าเกิดรูปแบบ polymorph solvate หรือ hydrate ของ VPU วิธีที่นำมาใช้ในการศึกษาไม่สามารถทำให้เกิดรูปแบบอสังฐานที่สมบูรณ์ของ VPU

การศึกษาความคงตัวในสภาวะของแข็งของ VPU ที่อุณหภูมิ 50-80 °C ในช่วงเวลาต่างๆ โดยนำตัวอย่างที่ได้มาวิเคราะห์โดยวิธี quantitative XRPD analysis โดยใช้โซเดียมคลอไรด์เป็นสารมาตรฐานภายใน พบว่ากลไกการเปลี่ยนแปลงของ VPU จากรูปแบบผลึกไปเป็นรูปแบบอสังฐานไม่สามารถอธิบายได้ด้วยกลไกเดียว แต่จำเป็นต้องคำนวณหาค่า activation energy ของกลไกที่เกิดขึ้น จากสมการของ Arrhenius พบว่า activation energy ที่ได้จากแต่ละสมการที่ใช้ในการศึกษาไม่แตกต่างกัน ดังนั้นจึงไม่สามารถตัดสินได้ว่ากลไกใดเป็นกลไกหลักที่เกิดขึ้น อย่างไรก็ตาม สรุปได้ว่าอัตราการเปลี่ยนแปลงของ VPU จะสูงขึ้นเมื่ออุณหภูมิสูงขึ้น

การศึกษาความสามารถในการละลายของ VPU พบว่า ตัวอย่างจากการศึกษาความคงตัวที่ 80 °C เป็นเวลา 4 สัปดาห์ ซึ่งมีความเป็นอสังฐานสูงที่สุดจะมีความสามารถในการละลาย สูงกว่า VPU มาตรฐาน 1.4 เท่า

ภาควิชา ..... เกษ์ชอุตสาหกรรม ..... ลายมือชื่อนิลิต ..... ๗๖๖๗๖ ๘๖๗๗๖๖  
 สาขาวิชา ..... เกษ์ชอุตสาหกรรม ..... ลายมือชื่ออาจารย์ที่ปรึกษา .....  
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KEYWORD: N (2-PROPYLPENTANOYL) UREA/SOLID STATE/SOLID PHASE TRANSFORMATION/  
AMORPHOUS/X-RAY POWDER DIFFRACTOMETRY

PASHARIN SIRIAROONRAT : SOLID STATE CHARACTERIZATION OF N (2-  
PROPYLPENTANOYL) UREA. THESIS ADVISOR : NARUEPORN SUTANTHAVIBUL, Ph.D.,

THESIS COADVISOR : ASSIST. PROF. CHAMNAN PATARAPANICH, Ph.D., 105 pp. ISBN

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Solid state chemical properties of N (2-propylpentanoyl) urea (VPU), a newly synthesized anticonvulsant compound, were investigated. Solid state characterization of VPU includes solid phase identification, solid state stability and solubility measurement.

Solid phase screening was investigated by treating reference VPU by various methods including recrystallization in several solvents, evaporation crystallization, immediate solidification from melt and thermal treatment. The products obtained were identified for their chemical integrity and purity using thin layer chromatography (TLC) and fourier transform infrared spectroscopy (FTIR) and phase characterization was done by x-ray powder diffraction (XRPD). Selected products were further determined by differential scanning calorimetry (DSC), thermogravimetry (TGA) and scanning electron microscopy (SEM). There were no differences in the XRPD patterns among the samples, except the product recrystallized from hexane and heptane by rapid solvent evaporation method (method I). DSC and TGA patterns among samples are also similar. As for the methods used to produce various solid phase, no evidence was found to support the existence of polymorph, solvate or hydrate form of VPU. The pure amorphous form cannot be achievable by any methods used in this study.

Solid state stability of VPU was studied over a temperature range of 50-80°C as a function of time. The samples obtained were determined by quantitative XRPD analysis with sodium chloride used as internal standard. It was found that the mechanism of the transformation from crystal form to amorphous form of VPU cannot be described by any particular model but the models were needed to calculate the activation energy. Using Arrhenius equation, activation energies obtained from all equations used were not significantly different. Therefore, the major transformation mechanism occurred was not observable. However, it could be summarized that the higher the temperature, the greater rate of transformation.

Solubility of VPU was determined. Solubility of the sample which exhibited maximum partialy amorphous phase when collected after 4 weeks at 80°C, was 1.4 times greater than the reference VPU.

Department	Manufacturing Pharmacy	Student's signature	<i>Pasharin Siriaronrat.</i>
Field of study	Industrial Pharmacy	Advisor's signature	<i>N. Sutanthavibul</i>
Academic year	2000	Co-advisor's signature	<i>Chamnana Patrapanich</i>



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**LIST OF ABBREVIATIONS**

cm	centimeter (s)
DSC	differential scanning calorimetry
$^{\circ}2\theta$	degree 2 theta
$^{\circ}\text{C}$	degree celcius (centigrade)
FTIR	fourier transform infrared spectroscopy
g	gram (s)
hr	hour (s)
KV	kilovolt
mA	milliampere (s)
mg	milligram (s)
min	minute (s)
ml	milliliter (s)
nm	nanometer (s)
$r^2$	correlation of determination
RH	relative humidity
rpm	revolution per minute
SD	standard deviation
SEM	scanning electron microscopy
T	absolute temperature
TGA	thermogravimetric analysis
TLC	thin layer chromatography
VPA	2-propylpentanoic acid (Valproic acid)
VPU	N-(2-propylpentanoyl) urea (Valproyl urea)
w/w	weight by weight
XRPD	x-ray powder diffraction