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# การเพิ่มการละลายของนิเฟดีพีนโดยโซลิดดิสเพอร์ชัน

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**ENHANCED DISSOLUTION OF NIFEDIPINE  
BY SOLID DISPERSION**

**Miss Nicha Khusakul**

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

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**Graduate School**

**Chulalongkorn University**

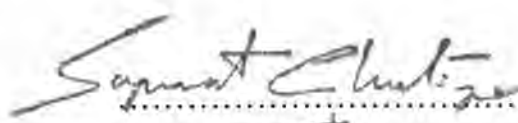
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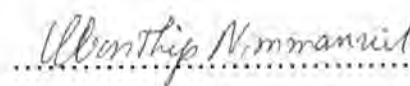
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By                      Miss Nicha Khusakul  
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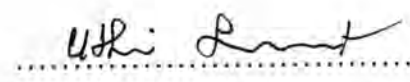
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ณิชา คุสกุล : การเพิ่มการละลายของนิเฟดิพีนโดยโซลิดดิสเพอร์ชัน

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การศึกษาของนิเฟดิพีนโซลิดดิสเพอร์ชัน โดยใช้ตัวพากลุ่มโพลีเอทิลีนไกลคอล (โพลีเอทิลีนไกลคอล 4000 และ 6000) กลุ่มโพลีลอกซาเมอร์ (โพลีลอกซาเมอร์ 188, โพลีลอกซาเมอร์ 288 และ โพลีลอกซาเมอร์ 407) และ กลุ่มโซโคเลเด็กซ์ทริน (บีต้าโซโคเลเด็กซ์ทริน และ 2-ไฮดรอกซีโพรพิลบีต้าโซโคเลเด็กซ์ทริน) โดยใช้อัตราส่วนของตัวยาคต่อตัวพา 4 อัตราส่วน คือ 1:1, 1:3, 1:5 และ 1:10 ในแต่ละระบบได้เตรียมโดยใช้วิธีการที่แตกต่างกัน 4 วิธี คือ การบดผสมทางกายภาพ การหลอมเหลว การใช้ตัวทำละลาย และการบดผสมเปียก

การละลายของนิเฟดิพีนจะเพิ่มขึ้นมากที่สุดเมื่อมีการกระจายตัวในกลุ่มตัวพาโพลีลอกซาเมอร์ ตามมาด้วยกลุ่มของโพลีเอทิลีนไกลคอล และโซโคเลเด็กซ์ทริน ในกลุ่มโพลีลอกซาเมอร์ เทคนิคที่ทำให้การละลายเพิ่มขึ้นชัดเจน คือ เทคนิคการหลอมเหลว และการละลายด้วยตัวทำละลาย การเพิ่มขึ้นของการละลายเรียงจากมากที่สุดไปหาน้อยที่สุด คือระบบโพลีลอกซาเมอร์ 188, โพลีลอกซาเมอร์ 288 และ โพลีลอกซาเมอร์ 407 ตามลำดับ ( $P < 0.05$ ) อัตราการละลายของโพลีเอทิลีนไกลคอล 4000 และโพลีเอทิลีนไกลคอล 6000 มีค่าใกล้เคียงกันมากเมื่อเปรียบเทียบระหว่างวิธีการเตรียม และอัตราส่วนที่ใช้เตรียมที่เหมือนกัน ในกลุ่มโพลีเอทิลีนไกลคอลนี้ วิธีการหลอมเหลว และการใช้ตัวทำละลายจะให้ค่าอัตราการละลายที่ดีที่สุดเช่นเดียวกับที่เกิดขึ้นในกลุ่มโพลีลอกซาเมอร์ สำหรับกลุ่มของบีต้าโซโคเลเด็กซ์ทริน และ 2-ไฮดรอกซีโพรพิล-บีต้าโซโคเลเด็กซ์ทริน ซึ่งเตรียมโดยวิธีการบดผสมเปียกและการใช้ตัวทำละลาย พบว่าไม่เกิดสารประกอบเชิงซ้อนของตัวยาคและตัวพา ดังจะเห็นได้จากค่าคงที่ของอัตราการละลายเพิ่มขึ้นเพียงเล็กน้อย พบว่าอัตราส่วนของตัวยาคและตัวพาที่มีค่า 1:10 ของระบบส่วนใหญ่จะให้ค่าอัตราการละลายสูงกว่าที่อัตราส่วนอื่น

กลุ่มโพลีลอกซาเมอร์ 188 ให้ค่าอัตราการละลายสูงสุดที่อัตราส่วนของยาต่อตัวพา 1:3 ซึ่ง เตรียมโดยวิธีการหลอมเหลวโดยพบว่าเวลาที่ใช้ในการละลายยา 80% เท่ากับ 15 นาที เมื่อเทียบกับยาบริสุทธิ์ซึ่งใช้เวลา 225 นาที กลไกสำคัญที่ทำให้มีการเพิ่มอัตราการละลายของนิเฟดิพีนในโพลีลอกซาเมอร์ คือ กลไกการเพิ่มค่าการละลาย และการเปียกน้ำของโพลีลอกซาเมอร์ และการเกิดเป็นอสังฐานของนิเฟดิพีน ซึ่งแสดงโดยเอกซ์เรย์ดิฟแฟรกชันและดิฟเฟอเรนเชียลสแกนนิ่งแคลอริเมตรี

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ลายมือชื่ออาจารย์ที่ปรึกษา .....  
ลายมือชื่ออาจารย์ที่ปรึกษาร่วม .....

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Solid dispersion of nifedipine in various carriers namely, polyethylene glycols (PEG4000 and PEG6000), poloxamers (poloxamer188, poloxamer288 and poloxamer407) and cyclodextrins ( $\beta$ -cyclodextrin and 2-hydroxypropyl- $\beta$ -cyclodextrin) at the drug-carrier ratio of 1:1, 1:3, 1:5 and 1:10 were investigated. The systems were prepared by four different methods which are physically mixed, melting, solvent and kneading methods.

The highest improved dissolution rate of nifedipine was found when solid dispersed in poloxamers, followed by secondly PEGs and lastly cyclodextrins. Among poloxamers, the distinctive methods are melting and solvent techniques. In general, the improved dissolution rates were ranked from the most to the least as poloxamer188, poloxamer288 and poloxamer407 systems respectively ( $p < 0.05$ ). PEG4000 and PEG6000 exhibited a very close value of dissolution rates when compared within the same method and ratio. Similarly to the poloxamers system, melting and solvent method are superior.  $\beta$ -Cyclodextrin and 2-hydroxypropyl- $\beta$ -cyclodextrin did not form inclusion complex with nifedipine hence showed only a slightly increase of dissolution rate constants. It was found that the drug-carrier ratio of 1:10 showed most conspicuous rates in most cases.

The highest dissolution rate was found in nifedipine-poloxamer188 at the drug-carrier ratio of 1:3 prepared by the melting method which gave the time at 80% dissolution of only 15 minutes compared with 225 minutes of the pure drug. The possible key mechanisms for improvement of nifedipine dissolution rates in poloxamers could be solubilizing effect, increasing wettability and amorphous transformation which shown via X-ray diffraction and differential scanning calorimetry.

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ลายมือชื่อนิสิต.....  
ลายมือชื่ออาจารย์ที่ปรึกษา.....  
ลายมือชื่ออาจารย์ที่ปรึกษาร่วม.....

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## LIST OF ABBREVIATIONS

°C	=	degree Celsius
2-HBCD	=	2-hydroxypropyl- $\beta$ -cyclodextrin
ANOVA	=	analysis of variance
BCD	=	$\beta$ -cyclodextrin
cm	=	centimeter
DSC	=	differential scanning calorimetry
g	=	gram
IR	=	infrared
KV	=	kilovolt
LSR	=	Least significant range
mA	=	milliamperere
mg	=	milligram
min	=	minute
ml	=	milliliter
mm	=	millimeter
nm	=	nanometer
PEG	=	polyethylene glycol
psi	=	pound per square inch
$r^2$	=	coefficient of determination
SEM	=	scanning electron microscopy
SMG	=	simulated gastric fluid without pepsin
SSR	=	Significant studentized ranges.
UV	=	ultraviolet
XRD	=	X-ray diffraction
$\mu$ g	=	microgram
$\mu$ m	=	micrometer