

การพัฒนายาเม็ดโคโลฟีแนคโซเดียมชนิดออกฤทธิ์นาน  
จากโซลิดดิสเพอร์ชันแบบพ่นแห้งด้วยวิธีอพติไมเซชัน



นายเพียรกิจ แดงประเสริฐ

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DEVELOPMENT OF DICLOFENAC SODIUM CONTROLLED  
RELEASE TABLET FROM SOLID DISPERSION BY SPRAY DRYING  
USING OPTIMIZATION METHOD



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## พิมพ์ตำลากับบทคัดย่อวิทยานิพนธ์ภายในกรอบสี่เหลี่ยมนี้เพียงแผ่นเดียว

เพียรกิจ แดงประเสริฐ : การพัฒนายาเม็ดไดโคลฟีแนคโซเดียมชนิดออกฤทธิ์นานจาก  
โซลิดดิสเพอร์ชันแบบพ่นแห้งด้วยวิธีออปติไมเซชัน (DEVELOPMENT OF DICLOFENAC  
SODIUM CONTROLLED RELEASE TABLET FROM SOLID DISPERSION BY SPRAY  
DRYING USING OPTIMIZATION METHOD) อ. ที่ปรึกษา : รศ.ดร. กาญจน์พิมล  
ฤทธิ์เดช, อ.ที่ปรึกษาร่วม : รศ.ดร. สุนิพนธ์ ภูมิมางกูร, 287 หน้า. ISBN 974-631-568-4

ไดโคลฟีแนคโซเดียมโซลิดดิสเพอร์ชันชนิดออกฤทธิ์นานซึ่งเตรียมจากการพ่นแห้งโดยใช้ตัวพา  
เดี่ยวคือ ethylcellulose (EC), methacrylic acid copolymer (Eudragit), chitosan,  
hydroxypropyl methylcellulose (HPMC), carbomer และตัวพาร่วมคือ EC-chitosan  
ในบรรดาระบบโซลิดดิสเพอร์ชันที่เตรียมขึ้นจากตัวพาและตัวพาเดี่ยวในอัตราส่วน 3:1 ระบบของ  
chitosan มีการละลายของยาช้าที่สุด รองลงมาได้แก่ระบบของ Eudragit, EC, HPMC และ  
carbomer ตามลำดับ ระบบที่ใช้ EC-chitosan เป็นตัวพาร่วมแสดงผลยับยั้งการละลายของยามากกว่า  
ระบบที่ใช้ EC หรือ chitosan ตามลำดับเป็นตัวพา

มาทริกซ์แบบ Hadamard H[8] ได้ใช้เพื่อประเมินผลของพารามิเตอร์สี่ประการได้แก่  
ปริมาณของของเหลวที่นำไปพ่นแห้ง ปริมาณของ absolute ethanol, EC และ chitosan  
ที่มีต่อการละลายของไดโคลฟีแนคโซเดียมโซลิดดิสเพอร์ชันซึ่งเตรียมจาก EC-chitosan ออปติไมเซชัน  
โดยอาศัยโปรแกรมคอมพิวเตอร์แบบการลดถอยพหุคูณเชิงเส้น และแบบ feasibility ได้ใช้กำหนด  
ปริมาณที่เหมาะสมของพารามิเตอร์เหล่านั้น สภาวะที่เหมาะสมในการเตรียมไดโคลฟีแนคโซเดียมโซลิดดิส  
เพอร์ชันโดยการพ่นแห้งซึ่งประกอบด้วยตัวยา 10 กรัม ได้แก่ ปริมาตรของของเหลวที่นำไปพ่นแห้ง  
200 มิลลิลิตร สัดส่วนของ absolute ethanol เท่ากับ 0.7 ปริมาณของ EC 2.5 กรัม และปริมาณ  
ของ chitosan 0.02 กรัม

ไดโคลฟีแนคโซเดียมโซลิดดิสเพอร์ชันที่เหมาะสมซึ่งเตรียมขึ้น ได้พัฒนาเป็นยาเม็ดโดยวิธี  
ตอกโดยตรง ออปติไมเซชันโดยอาศัยการออกแบบการทดลองแบบ central composite และ  
การลดถอยพหุคูณได้ใช้เพื่อศึกษาอิทธิพลของพารามิเตอร์สี่ประการ ที่มีต่อคุณสมบัติทางกายภาพและ  
การละลายของยาเม็ด พารามิเตอร์ดังกล่าวได้แก่ แรงที่ใช้ตอกยา ปริมาณของแป้งข้าวเจ้าชนิดพ่นแห้ง  
(Era-Tab<sup>®</sup>) ปริมาณของ croscarmellose sodium (Ac-Di-Sol<sup>®</sup>) และปริมาณของ magnesium  
stearate ได้ทำการค้นหาปริมาณที่เหมาะสมของพารามิเตอร์ดังกล่าว และนำไปตั้งตำรับยาเม็ดไดโคล  
ฟีแนคโซเดียมชนิดออกฤทธิ์นานที่เหมาะสม สภาวะที่เหมาะสมสำหรับผลิตยาเม็ดดังกล่าวซึ่งประกอบด้วย  
ตัวยา 100 มิลลิกรัมได้แก่ แรงที่ใช้ตอก 700 ปอนด์ต่อตารางนิ้ว ปริมาณ Era-Tab 194.8 มิลลิกรัม  
ต่อเม็ด ปริมาณ Ac-Di-Sol 6.4 มิลลิกรัมต่อเม็ด และปริมาณ magnesium stearate 1.6  
มิลลิกรัมต่อเม็ด

ไดโคลฟีแนคโซเดียมโซลิดดิสเพอร์ชัน และยาเม็ดไดโคลฟีแนคชนิดออกฤทธิ์นานที่เหมาะสม  
ได้ยืนยันถึงความถูกต้องโดยการวิเคราะห์เชิงสถิติ ลักษณะการละลายของทั้งสองที่ได้จากการทดลอง  
เมื่อเทียบกับลักษณะการละลายที่ทำนายไว้ พบว่าอยู่ในขอบเขตของระดับความเชื่อมั่น 99% ลักษณะการ  
ละลายของยาเม็ดที่เหมาะสมคล้ายคลึงกับที่ได้จากโซลิดดิสเพอร์ชันที่เหมาะสม Scanning electron  
microscope, differential thermal analysis และ X-ray diffraction ได้ใช้เพื่อศึกษา  
ความสมบูรณ์ของการเกิดโซลิดดิสเพอร์ชัน กลไกในการปลดปล่อยตัวยาจากทั้งไดโคลฟีแนคโซเดียมและ  
ยาเม็ดที่เหมาะสมคือการควบคุมโดยการแพร่

ภาควิชา.....เภสัชกรรม-เภสัชอุตสาหกรรม  
สาขาวิชา.....เภสัชกรรม  
ปีการศึกษา.....2537

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

## C375377 : MAJOR PHARMACEUTICS

KEY WORD: DICLOFENAC SODIUM/ SOLID DISPERSION/ SPRAY DRY/ OPTIMIZATION/ CONTROLLED RELEASE  
PIENKIT DANGPRASIRT : DEVELOPMENT OF DICLOFENAC SODIUM CONTROLLED RELEASE TABLET  
FROM SOLID DISPERSION BY SPRAY DRYING USING OPTIMIZATION METHOD. THESIS ADVISOR :  
ASSO. PROF. GARNPIMOL C. RITTHIDEJ, Ph.D., THESIS CO-ADVISOR : ASSO. PROF.  
SUNIBHOND PUMMANGURA, Ph. D. 287 pp. ISBN 974-631-568-4

Diclofenac sodium (DS) controlled release solid dispersions were prepared by spray drying using ethylcellulose (EC), methacrylic acid copolymer (Eudragit), chitosan, hydroxypropyl methylcellulose (HPMC), and carbomer as single carriers and EC-chitosan as combined carriers. Among solid dispersions of 3:1 drug:single carrier, the system of chitosan exhibited the slowest dissolution followed by the systems of Eudragit, EC, HPMC, and carbomer, respectively. Combined carriers of EC-chitosan exhibited higher dissolution retarding effect than single carrier of EC or chitosan.

An Hadamard matrix H[8] was employed to estimate the main effects of four parameters; spray feeding volume and contents of absolute ethanol, EC, and chitosan, on dissolution of DS:(EC+chitosan) solid dispersions. Optimization strategy using multiple linear regression and a feasibility computer program was utilized to obtain the optimum quantities of the four parameters that would result in a required DS controlled release solid dispersion. An optimum set of conditions for preparing spray-dried DS controlled release solid dispersion, containing 10 g of drug, were spray feeding volume of 200 ml, absolute ethanol fraction of 0.7, ethylcellulose content of 2.5 g, and chitosan content of 0.02 g.

The optimum DS solid dispersion was prepared and formulated into tablet dosage form by direct compression. Optimization strategy using a central composite design and multiple regression was used to study the influences of four parameters; compression force, the amount of spray-dried rice starch (Era-Tab<sup>®</sup>), croscarmellose sodium (Ac-Di-Sol<sup>®</sup>), and magnesium stearate, on tablet physical properties and dissolution. The optimum conditions of those parameters were searched and an optimum DS controlled release tablet formulation was formulated. An optimum condition in preparing DS controlled release tablet, containing 100 mg of drug, was found to be compression force of 700 psi, Era-Tab content of 194.8 mg per tablet, Ac-Di-Sol content of 6.4 mg per tablet, and magnesium stearate content of 1.6 mg per tablet.

The optimum DS solid dispersion and tablet were prepared and validated by statistical analysis. Their experimental dissolution profiles lied almost completely within the 99% confidence band of their predicted dissolution profiles. The dissolution profile of the optimized DS controlled release tablet was similar to that of the optimized DS controlled release solid dispersion. Scanning electron microscope, differential thermal analysis and X-ray diffraction were used to study the completion of solid dispersion formation. The mechanisms of drug release from the optimum DS controlled release solid dispersion and tablet were found to be diffusion controlled.

ภาควิชา เกษษกรรม-เภสัชอุตสาหกรรม  
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## ABBREVIATIONS

°C	celcius degree
cc	cubic centimeter
cps	centripoise
Cu	Copper
DTA	differential thermal analysis
DS	Diclofenac sodium
EC	Ethylcellulose
g	gram
HPMC	Hydroxypropyl methylcellulose
hr	hour
kV	kilo volt
mg	milligram
min	minute
ml	milliliter
N	normal
nm	nanometer
psi	pound per square inch
rpm	revolution per minute
UV	ultraviolet
μg	microgram
μV	microvolt