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**CONTROLLED RELEASE THEOPHYLLINE GRANULES COATED WITH
POLY (ETHYLACRYLATE METHYLMETHACRYLATE)
AQUEOUS DISPERSION BY FLUIDIZED BED TECHNIQUE**



Miss Uraiwan Petcharunpaisan

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จุฬาลงกรณ์มหาวิทยาลัย**
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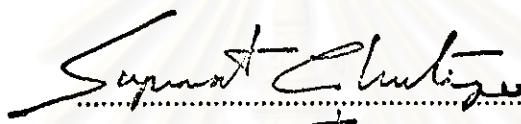
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อุไรวรรณ เพชรจรัสไพศาล : ทีโอฟิลลีนแกรนูลชนิดควบคุมการปลดปล่อยตัวยาที่เคลือบด้วยสารโพลี (เอธิลอะคริเลต เมธิลเมทาคริเลต) ชนิดกระจายตัวในน้ำ โดยเทคนิคฟลูอิดไลซ์เบด (CONTROLLED RELEASE THEOPHYLLINE GRANULES COATED WITH POLY(ETHYLACRYLATE METHYLMETHACRYLATE) AQUEOUS DISPERSION BY FLUIDIZED BED TECHNIQUE) อ.ที่ปรึกษา : รศ.ดร. กาญจน์ทิมม ฤทธิเดช. อ.ที่ปรึกษาร่วม : ผศ. วิเชียร ธานินทร์ธรราร , 178 หน้า. ISBN 974-637-103-7

การเคลือบทีโอฟิลลีนแกรนูลขนาด 18/20 เมชด้วยซูครราจิด เอ็น อี 30ดี [โพลี (เอธิลอะคริเลต เมธิลเมทาคริเลต) เอเควีคอสติสเพอซัน] ซึ่งมีแคปโซลิตผสมอยู่เป็นสารกันติด โดยใช้เทคนิคการพ่นเคลือบแบบฟลูอิดไลซ์เบด รวมทั้งอัตราส่วนต่าง ๆ ของซูครราจิด เอ็น อี 30ดี คอไฮดรอกซีโพรพิลเมธิลเซลลูโลส ซึ่งเป็นพอลิเมอร์ที่ไม่มีประจุและละลายน้ำได้ และซูครราจิด เอ็น อี 30ดี คอซูครราจิด ฮาร์ แอด 30ดี (แอมโมนิโอเมทาคริเลต โคลอติเมอร์ ชนิดเอ) ซึ่งเป็นพอลิเมอร์ที่มีประจุบวกและละลายน้ำไม่ได้แต่มีความสามารถในการซึมผ่านที่สูงกว่า เพื่อศึกษาคุณสมบัติทางกายภาพและคุณสมบัติการปลดปล่อยยาจากแกรนูลที่ถูกเคลือบแล้ว รวมทั้งอิทธิพลของตัวแปรในกระบวนการผลิตซึ่งได้แก่วิธีพ่นและแรงดันอัดอากาศ พื้นผิวของแกรนูลที่เคลือบด้วยซูครราจิด เอ็น อี 30ดีทั้งหมดจะมีลักษณะที่เรียบกว่าพื้นผิวของแกรนูลที่ไม่ได้เคลือบ การเพิ่มระดับการเคลือบจะทำให้ความหนาของฟิล์มเพิ่มขึ้นดังนั้นอัตราการปลดปล่อยตัวยาจะลดลง พื้นผิวของแกรนูลที่เคลือบด้วยซูครราจิด เอ็น อี 30ดี รุ่นบี จะมีลักษณะขรุขระและมีรูพรุนมากกว่าแกรนูลที่เคลือบด้วยซูครราจิด เอ็น อี 30ดี รุ่นเอ ส่งผลให้มีอัตราการปลดปล่อยตัวยาที่มากกว่าเนื่องมาจากความคงตัวของพอลิเมอร์ วิธีพ่นมีผลต่อลักษณะพื้นผิวและอัตราการไหลของแกรนูลอย่างเด่นชัดแต่ทั้งวิธีพ่นจากด้านบนและด้านล่างจะให้ลักษณะการปลดปล่อยตัวยาที่คล้ายคลึงกัน เนื่องจากการเคลื่อนที่ที่แตกต่างกันของอนุภาคในระหว่างกระบวนการเคลือบ แรงดันอัดอากาศที่สูงกว่าจะให้ฟิล์มที่มีลักษณะที่ไม่ต่อเนื่อง อาจเนื่องมาจากการลดลงของอุณหภูมิภายในห้องเคลือบซึ่งนำไปสู่การเกิดฟิล์มที่ไม่เหมาะสม ดังนั้นจึงมีการละลายของยาที่สูงกว่า การเติมไฮดรอกซีโพรพิลเมธิลเซลลูโลสจะให้ผิวที่พรุนน้อยลงและมีความเรียบเพิ่มขึ้น ในขณะที่การเติมซูครราจิด ฮาร์ แอด 30ดี จะได้ผิวที่พรุนคล้ายฟองน้ำ พอลิเมอร์ทั้งสองจะเพิ่มการละลายของยาอย่างชัดเจน แกรนูลที่เคลือบด้วยซูครราจิด เอ็น อี 30ดี รุ่นเอ 4.66 % และรุ่นบี 13.51 % จะให้การปลดปล่อยตัวยาตามข้อกำหนดของทีโอฟิลลีนชนิดแคปซูลออกฤทธิ์นานของเภสัชตำรับสหรัฐอเมริกา



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สาขาวิชาเภสัชอุตสาหกรรม.....
ปีการศึกษา2540.....

ลายมือชื่อนิสิตอุไรวรรณ เพชรจรัสไพศาล.....
ลายมือชื่ออาจารย์ที่ปรึกษา
ลายมือชื่ออาจารย์ที่ปรึกษาร่วม

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KEY WORD: THEOPHYLLINE / CONTROLLED RELEASE / POLY (ETHYLACRYLATE METHYLMETHACRYLATE) AQUEOUS DISPERSION / FLUIDIZED BED
URAIWAN PETCHARUNPAISAN : CONTROLLED RELEASE THEOPHYLLINE GRANULES COATED WITH POLY (ETHYLACRYLATE METHYLMETHACRYLATE) AQUEOUS DISPERSION BY FLUIDIZED BED TECHNIQUE. THESIS ADVISOR :
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Theophylline granules of 18/20 mesh size were coated with different level and lot of Eudragit® NE 30D [poly(ethylacrylate methylmethacrylate) aqueous dispersion] containing Cab-O-Sil as an antiadherent by fluidized bed technique. Different ratios of Eudragit® NE 30D to hydroxypropylmethylcellulose, a nonelectrolyte, water soluble polymer, or to Eudragit® RL 30D (ammonio methacrylate copolymer, type A), a cationic water insoluble but higher permeable polymer, were also employed. The physical properties and the drug release characteristics of coated granules were evaluated. The influences of processing variable, spraying method and atomizing air pressure, were also studied.

All Eudragit® NE 30D coated granules exhibited smoother surface than uncoated granules. Increasing the level of coating increased the thickness of film, thus the rate of drug release was decreased. Eudragit® NE 30D lot B produced rougher and more porous surface coating film than lot A which led to higher release rate, probably due to the polymer stability. The mode of spray apparently affected the surface characteristics and the flow rates of coated granules but both top spray and bottom spray method caused similar drug release characteristic. This result might be due to differences in the particle motion during the coating process. Higher atomizing air pressure gave less continuous characteristic of film coating probably due to the decreasing temperature in coating chamber which might not be conducive to optimum film formation. Thus, higher drug dissolution was obtained.

Addition of hydroxypropylmethylcellulose caused less porous and smoother surface whereas Eudragit® RL 30D caused more porous and sponge-like surface. Both polymers dramatically increased the drug dissolution. The release of drug from granules coated with 4.66 % Eudragit® NE 30D lot A and 13.51 % Eudragit® NE 30D lot B could conform to the monograph of extended-release theophylline capsules in USP XXIII.

ภาควิชา.....เภสัชอุตสาหกรรม.....

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LIST OF ABBREVIATIONS

| | |
|----------------|--|
| bar | kg/cm ² |
| °C | degree celsius (centigrade) |
| cm | centimetre (s) |
| EA | ethylacrylate |
| e.g. | exempli gratia, for example |
| et al. | et alii, and others |
| g | gram (s) |
| GI | gastrointestinal |
| HPMC | hydroxypropylmethylcellulose |
| HPLC | high performance liquid chromatography |
| hr | hour (s) |
| i.e. | id est, that is |
| IR | infrared |
| m ² | square metre (s) |
| MFT | minimum film-forming temperature |
| min. | minute (s) |
| mg | milligram (s) |
| ml | millilitre (s) |
| mm | millimetre (s) |
| MMA | methylmethacrylate |
| N | normality |
| nm | nanometre (s) |
| pH | the negative logarithm of the hydrogen ion concentration |
| qs. | make to volume |
| r ² | coefficient of determination |
| % RH | percentage of relative humidity |

| | |
|-------|--|
| rpm | revolution per minute |
| sec. | second (s) |
| SD | standard deviation |
| SEM | scanning electron photomicrograph |
| TAMCI | trimethylammonioethylmethacrylate chloride |
| USP | The United States Pharmacopoeia |
| UV | ultraviolet |
| w/w | weight by weight |
| w/v | weight by volume |
| µg | microgram (s) |
| µl | microlitre (s) |
| µm | micrometre (s), micron (s) |



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