

ขำม่คอกฤทธีน่านแบบหลายหน่วยของคิลไทอะเซมไฮโครคลอไรด์เรซินเทคนิคเคลือบฟิล์ม



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MULTIPLE-UNIT SUSTAINED RELEASE TABLETS OF FILM-COATED
DILTIAZEM HYDROCHLORIDE RESINATES

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อัญญาวี เค่นสรศิริ : ยามีคออกฤทธิ์นานแบบหลายหน่วยของดิลไทอะเซมไฮโดรคลอไรด์เรซินชนิดเคลือบฟิล์ม (MULTIPLE-UNIT SUSTAINED RELEASE TABLETS OF FILM-COATED DILTIAZEM HYDROCHLORIDE RESINATES) อาจารย์ที่ปรึกษา : รศ.ดร.พจน์ กุลวานิช, 145 หน้า

วัตถุประสงค์ของงานวิจัยนี้เพื่อศึกษาการเตรียมยามีคออกฤทธิ์นานแบบหลายหน่วยของดิลไทอะเซมไฮโดรคลอไรด์เรซินชนิดเคลือบฟิล์มบรรจุด้วยดิลไทอะเซมไฮโดรคลอไรด์ใน sulfonic acid cation exchange resin ได้แก่ Dowex[®] 88 เรซินที่มีระดับการเชื่อมขวาง 4 % และ Dowex[®] HCR-S เรซินที่มีระดับการเชื่อมขวาง 8 % โดยวิธี batch method ศึกษาปัจจัยที่มีผลต่อการบรรจุด้วยในเรซิน ได้แก่ ระดับการเชื่อมขวางของเรซิน ปริมาณเรซินที่ใช้ในการบรรจุด้วย ความเข้มข้นของสารละลายยา และอุณหภูมิระหว่างการบรรจุด้วย พบว่าปริมาณยาที่บรรจุในเรซินที่มีระดับการเชื่อมขวาง 4 % เท่ากับ 28.80 % สูงกว่าในเรซินที่มีระดับการเชื่อมขวาง 8 % ซึ่งสามารถบรรจุด้วยได้เพียง 5.51 % ปริมาณยาที่บรรจุในเรซินจะลดลงเมื่อปริมาณเรซินที่ใช้ในการบรรจุด้วยเพิ่มขึ้น สภาวะที่เหมาะสมมากที่สุดในการเตรียมเรซินคือการเตรียมสารละลายตัวยาขณะบรรจุในความเข้มข้น 8 % โดยน้ำหนัก โดยใช้อัตราส่วนระหว่างตัวยาและเรซินในอัตราส่วนหนึ่งต่อหนึ่ง นอกจากนี้การเพิ่มอุณหภูมิที่ควบคุมระหว่างการบรรจุด้วยมีผลให้ปริมาณยาที่บรรจุในเรซินเพิ่มขึ้นและทำให้ระบบเกิดสมดุลเร็วขึ้น การทดลองการปลดปล่อยตัวยาในสารละลาย 0.1 โมลาร์โพแทสเซียมคลอไรด์ พบว่าเรซินสามารถควบคุมการปลดปล่อยตัวยาได้นานถึง 12 ชั่วโมง จลนศาสตร์ของการปลดปล่อยตัวยาออกจากเรซินสามารถอธิบายได้ด้วยรูปแบบการแพร่ของอนุภาคตัวยาผ่านเมมเบรน โดยการปลดปล่อยตัวยาออกจากเรซินขึ้นกับความเข้มข้นของไอออนบวกในสารละลายตัวกลาง ในขณะที่ pH ของสารละลายตัวกลางมีผลน้อยมาก การเคลือบเรซินด้วยอะครีลิกเอทิลเมออร์โดยเทคนิคฟลูอิด ไคซ์เบดสามารถชะลอการปลดปล่อยตัวยาให้ช้าลง โดยการเคลือบเรซินด้วย 7.5-15 % Eudragit[®] RL และ Eudragit[®] RS ไม่มีผลต่อจลนศาสตร์ของการปลดปล่อยตัวยา เมื่อนำเรซินที่เคลือบฟิล์มมาเตรียมเป็นยามีคโดยใช้แรงตอกอัดในช่วง 340-1,022 ปอนด์ พบว่าเม็ดยาที่เตรียมจากการผสมเรซินกับแกรนูลของไมโครคริสตัลลินเซลลูโลสและพอลิเอทิลีนไกลคอล 4000 มีคุณสมบัติทางกายภาพที่ดี มีรูปแบบการปลดปล่อยตัวยาและจลนศาสตร์ของการปลดปล่อยตัวยาไม่แตกต่างกับรูปแบบการปลดปล่อยตัวยาจากเรซินก่อนตอก

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AUNYAVEE DENSORNISIRI : MULTIPLE-UNIT SUSTAINED RELEASE
TABLETS OF FILM-COATED DILTIAZEM HYDROCHLORIDE RESINATES.
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The objective of this study was to prepare the multiple-unit sustained release tablet of film-coated diltiazem hydrochloride resins. Diltiazem hydrochloride (DTZ) was loaded in sulfonic acid cation exchange resins, Dowex®88 4 % crosslinkage and Dowex®HCR-S 8 % crosslinkage by batch method. The factors affecting drug loading were investigated such as resin crosslinkage, quantity of resins, drug loading solution concentration and temperature during drug loading process. The DTZ bound in 4 % crosslinkage resins was 28.80 % which was higher than in an 8 % crosslinkage resin which was only 5.51 %. The percentage of DTZ loading in the resins decreased when the quantity of resins in the drug loading solution was increased. The drug resin in the ratio of 1:1 in 8 % w/v drug loading solution was suitable for preparing resins. Increasing in temperature increased the percentage of DTZ loading and reduced the time required for system to reach equilibrium. The resins could prolong DTZ release over 12 hours in 0.1 M potassium chloride solution. The release kinetic of resins was best described by the Matrix-diffusion controlled model (Higuchi model). The release rate was influenced by the ionic strength of dissolution medium, while the pH of dissolution medium did not. To modify drug release from resins, they were coated with acrylate polymer by using fluidized bed coating technique. Coating with 7.5-15 % coating level of Eudragit®RL and Eudragit®RS decreased the drug release rate but did not affect the drug release kinetic. Coated resins were formulated into disintegrating tablets and compressed at compression pressure between 340-1,022 pounds. Tablets formulated using microcrystalline cellulose and polyethylene glycol 4000 exhibited good physical properties. Drug release of resin before and after formulated into disintegrating tablets was similar. The release kinetic of drug from disintegrating tablets was also described by the Higuchi model.

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LIST OF ABBREVIATIONS

%	percentage
°C	degree Celsius (centigrade)
µg	microgram (s)
µm	micrometer (s)
CaCl ₂	calcium chloride
cm	centimeter (s)
DI	deionized
DTZ	diltiazem hydrochloride
et.al.	et alli, and others
gm	gram (s)
HPLC	high-performance liquid chromatography
hr	hour (s)
IR	infrared
KCl	potassium chloride
log	logarithm
mg	milligram (s)
min	minute (s)
ml	milliliter (s)
M	molarity
MW	molecular weight
NaCl	sodium chloride
pH	the negative logarithm of the hydrogen ion concentration
R ²	coefficient of determination
rpm	revolution (s) per minute
SD	standard deviation
SEM	scanning electron microscope
w/v	weight by volume
w/w	weight by weight