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PREPARATION AND CONTROLLED RELEASE OF
POLY(LACTIDE-CO-GLYCOLIDE) CONTAINING NICOTINE

Miss Wilasinee Robroo

A Thesis Submitted in Partial Fulfillment of the Requirements
for the Degree of Master of Science Program in Petrochemistry and Polymer Science

Faculty of Science

Chulalongkorn University

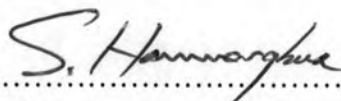
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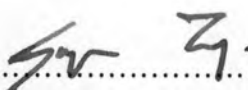
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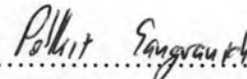
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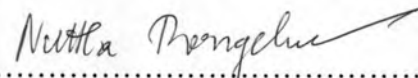
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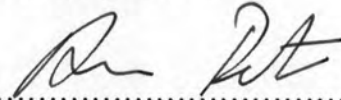

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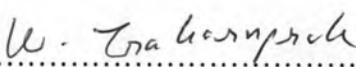
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วิลาสินี รอบรู้ : การเตรียมและการปลดปล่อยแบบควบคุมของพอลิแลกไทด์-โกลโคไลด์ ที่มีนิโคติน. (PREPARATION AND CONTROLLED RELEASE OF POLY (LACTIDE-CO-GLYCOLIDE) CONTAINING NICOTINE) อ. ที่ปรึกษา: รศ. ดร. พลกฤษณ์ แสงวณิช, อ. ที่ปรึกษาร่วม: ดร. ญัฐฐา ทองจุล, 99 หน้า.

ปัจจุบันได้มีการนำนิโคตินทดแทนมาใช้อย่างกว้างขวางเพื่อรักษาผลของการเลิกบุหรี่ในระหว่างการหยุดสูบบุหรี่ แผ่นติดผิวหนังนิโคตินใช้ได้ง่ายสำหรับผู้ป่วย อย่างไรก็ตามสามารถก่อให้เกิดการบวมและคันในบริเวณที่ปิดด้วยแผ่นติดผิวหนัง อาการเหล่านี้อาจมาจากสาเหตุการไม่เข้ากันกับวัสดุสารยึดติดที่ใช้ในแผ่นติดผิวหนัง การใช้วัสดุทางธรรมชาติสามารถช่วยขจัดปัญหานี้ ตัวอย่างเช่น การนำพอลิแลกไทด์-โกลโคไลด์ (PLLGA) มาใช้ในการเตรียมการปลดปล่อยแบบควบคุมของนิโคตินแผ่นติดผิวหนังในการศึกษานี้ พอลิแลคติก แอซิด (PLLA) น้ำหนักโมเลกุลต่ำสามารถเตรียมจากปฏิกิริยาพอลิเมอไรเซชันแบบควบแน่นของกรดแลคติก จากนั้นจึงสังเคราะห์แอล-แลกไทด์จากการสลายด้วยความร้อนของ PLLA โมเลกุลต่ำ หลังจากนั้นเตรียม PLLGA โคพอลิเมอร์โดยปฏิกิริยาพอลิเมอไรเซชันแบบเปิดวง (ROP) ของแอล-แลกไทด์และโกลโคไลด์ ใช้อัตราส่วน โมลาร์ของแอล-แลกไทด์และโกลโคไลด์ที่ต่างกัน โดยศึกษาผลของชนิดและความเข้มข้นของตัวเร่งปฏิกิริยา ระยะเวลาพอลิเมอไรเซชัน อุณหภูมิ และ อัตราส่วน โมลาร์ของแอล-แลกไทด์ และโกลโคไลด์ จากนั้นเตรียมฟิล์มโคพอลิเมอร์ PLLGA กับพอลิไวนิลแอลกอฮอล์ (PVA) พบว่าอัตราส่วน 0.5PLLGA/2PVA และ 1.5PLLGA/2PVA ที่สัดส่วน แอล-แลกไทด์/โกลโคไลด์ โคพอลิเมอร์ 70/30 ให้การปลดปล่อยนิโคตินน้อยและมากที่สุดที่ 738 และ 5,072 ไมโครกรัมต่อตารางเซนติเมตรต่อชั่วโมง ตามลำดับ แผ่นฟิล์ม PLLGA ผสม PVA ที่มี 1.5PLLGA/2PVA ที่สัดส่วนโคพอลิเมอร์ 70/30 มีปริมาณของการปลดปล่อยนิโคตินเหมือนกับแผ่นติดผิวหนังทางการค้า เพราะฉะนั้นจึงเหมาะสมที่จะถูกใช้ในบุคคลผู้ซึ่งมีความต้องการหยุดการสูบบุหรี่

สาขาวิชา.....ปีโทรเคมีและวิทยาศาสตร์พอลิเมอร์.....ลายมือชื่อนิสิต วิลาสินี รอบรู้.....

ปีการศึกษา2550.....

ลายมือชื่ออาจารย์ที่ปรึกษา พลกฤษณ์ แสงวณิช.....

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KEY WORD: NICOTINE, POLY(L-LACTIDE-CO-GLYCOLIDE) / RING
OPENING POLYMERIZATION / CONTROLLED RELEASE

WILASINEE ROBROO: PREPARATION AND CONTROLLED RELEASE
OF POLY(LACTIDE-CO-GLYCOLIDE) CONTAINING NICOTINE.
THESIS ADVISOR: ASSOC. PROF. POLKIT SANGVANICH, Ph.D.,
THESIS COADVISOR: NUTTHA THONGCHUL, Ph.D., 99 pp.

Nicotine replacement therapy is widely used to treat nicotine withdrawal during smoking cessation. Nicotine transdermal patches, easily used by patients, can however cause swelling and itching in the area covered by the patch. These symptoms are perhaps caused by non-biocompatible adhesive material used in patches. To eliminate this problem, biomaterial for example, poly(L-lactic-co-glycolide) (PLLGA) was used in the preparation of controlled released nicotine transdermal patches in this study. Low molecular weight of poly(L-lactic acid) (low MW PLLA) was prepared by condensation polymerization of lactic acid. L-lactide was synthesized from thermal decomposition of low MW PLLA. Later, PLLGA copolymer was prepared by ring opening polymerization (ROP) of L-lactide and glycolide using different L-lactide and glycolide molar ratios. The effects of type and concentration of catalyst, polymerization time, temperature and molar ratio of L-lactide and glycolide were studied. Poly (vinyl alcohol) PVA was used in preparation with PLLGA copolymer film. It appears that the ratio of 0.5PLLGA/2PVA and 1.5PLLGA/2PVA at the L-lactide/glycolide copolymer molar ratio of 70/30 provided the minimum and maximum nicotine release of 738 and 5,072 $\mu\text{gcm}^{-2}\text{h}^{-1}$, respectively. The PLLGA blended PVA film containing 0.5PLLGA/2PVA at the L-lactide/glycolide copolymer ratio of 70/30 has the amount of nicotine release similar to that in marketed transdermal patch. Therefore it is suitable to be used in people who would like to stop smoking.

Field of Study:..Petrochemistry and Polymer Science..Student's Signature: *Wilasinee Robroo*

Academic Year :.....2007.....

Advisor's Signature: *Polkit Sangvanich*

Co-advisor's Signature: *Nuttha Thongchul*

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LIST OF ABBREVIATIONS AND SYMBOLS

mg/kg	Milligram by kilogram
mg	Milligram
g	Gram
NRT	Nicotine replacement therapy
PLA	Poly lactide
PLLA	Poly(L-lactide)
PDLA	poly(D-lactide)
PGA	Polyglycolide
PLGA	Poly(lactic-co-glycolic acid)
PLLGA	Poly(L-lactic-co-glycolic acid)
Mw	Molecular weight
mg/cm ²	Milligram by square meter
µg/cm ²	Microgram by square meter
SEM	Scanning electron microscope
UV-VIS	Ultraviolet-visible
°C	Degree celsius
PSA	Pressure sensitive adhesive
TDS	Transdermal drug delivery systems
AHA	Alpha hydroxy acid
T _g	Glass transition temperature
T _m	Melting temperature
g/ml	Gram by milliliter
mmHg	Millimeters of mercury
ROP	Ring opening polymerization
CROP	Cationic ring opening polymerization
AROP	Anionic ring opening polymerization
w/w	Weight by weight
w/v	Weight by volume
PVA	Poly(vinyl alcohol)
DCM	Dichloromethane
wt%	Weight percentage

$\mu\text{gcm}^{-2}\text{h}^{-1}$	Microgram by square meter by hour
gmol^{-1}	Gram by mole
NMR	Nuclear Magnetic Resonance Spectrometer
DSC	Differential Scanning Calorimeter
GPC	Gel Permeation Chromatograph
mmol	Millimole
MHz	Megahertz
ppm	Part per million
TMS	Tetramethylsilane
THF	Tetrahydrofuran
mm	Millimeter
μm	Micrometer
ml/min	Milliliter per minute
μl	Microliter
$^{\circ}\text{C}/\text{min}$	Celsius degree by minute
v/v	Volume by volume
GD	Glutaraldehyde
cm	Centimeter
PBS	Phosphate buffered saline
S_w	Swelling degree
W_t	Weight at time
W_o	Initial weight
t	Time
$\mu\text{g}/\text{ml}$	Microgram by milliliter
nm	Nanometer
\overline{M}_w	Weight average molar mass
\overline{M}_n	Number average molar mass
PDI	Polydispersity
S.D.	Standard deviation