

การตั้งตำรับโคโตซานไมโครสเฟียร์ที่บรรจุดีออกซีซัยคลินโดยใช้กลีเซอรอลโมโนโอเลอิต
เป็นระบบนำส่งยาเพื่อรักษาโรคปริทันต์อักเสบ



นางสาวชนิษฐา สิงห์หิรัญนุสรณ์

วิทยานิพนธ์นี้เป็นส่วนหนึ่งของการศึกษาตามหลักสูตรปริญญาเภสัชศาสตรมหาบัณฑิต
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**FORMULATION OF DOXYCYCLINE LOADED CHITOSAN
MICROSPHERES IN GLYCERYL MONOOLEATE-BASED
DRUG DELIVERY SYSTEMS FOR PERIODONTITIS**

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ชินษรฐา สิงห์วีรญุสนธรม์: การดั่งตำรับไคโตซานไมโครสเฟียร์ที่บรรจุด็อกซีซัยคลินโดยใช้กลีเซอรอลโมโนโอเลตเป็นระบบนำส่งยาเพื่อรักษาโรคปริทันต์อักเสบ. (FORMULATION OF DOXYCYCLINE LOADED CHITOSAN MICROSPHERES IN GLYCERYL MONOOLEATE-BASED DRUG DELIVERY SYSTEMS FOR PERIODONTITIS) อาจารย์ที่ปรึกษา : รศ.ดร. สุชาดา ชุติมาวารพันธ์ อาจารย์ที่ปรึกษาร่วม : รศ. อาริรัตน์ ลออปักษา, 182 หน้า.

การศึกษานี้มีวัตถุประสงค์เพื่อดั่งตำรับไคโตซานไมโครสเฟียร์ที่บรรจุด็อกซีซัยคลินโดยใช้กลีเซอรอลโมโนโอเลตเป็นระบบนำส่งยาเพื่อใช้ในการรักษาโรคปริทันต์อักเสบ โดยสามารถเตรียมไคโตซานไมโครสเฟียร์ได้โดยวิธีการทำอิมัลชันและการเกิดเจลแบบใช้ไอออน ได้ใช้การออกแบบการทดลองแบบบ็อกซ์เบห์นเคนเพื่อหาสูตรที่มีความเหมาะสมที่สุด จากผลการทดลองได้เลือกสูตรตำรับที่เหมาะสมซึ่งประกอบด้วยด็อกซีซัยคลินไฮคลอเต (%) ไคโตซาน (%) และ โซเดียมไทรโพลฟอสเฟต (เอสทีพีพี) (%) เท่ากับ 75:3:15, 75:4:10 และ 30:3:10 ไมโครสเฟียร์ที่ได้สามารถปลดปล่อยด็อกซีซัยคลินไฮคลอเตได้นาน 24 ชั่วโมงและมีจลนศาสตร์การปลดปล่อยเป็นไปตามรากที่สองของเวลาซึ่งบ่งชี้ว่าอัตราการปลดปล่อยถูกควบคุมโดยการแพร่ การศึกษาความคงตัวแบบเร่งที่อุณหภูมิ 40, 50, 60 และ 70 องศาเซลเซียสและการพอลิโดแบบอาร์เรเนียส แสดงให้เห็นว่าไมโครสเฟียร์ที่ประกอบด้วยด็อกซีซัยคลินไฮคลอเต (%) ไคโตซาน (%) และเอสทีพีพี (%) เท่ากับ 75:3:15, 75:4:10 และ 30:3:10 มีอายุคุณภาพจากการทำนายเท่ากับ 47.04, 245.65 และ 22,208.38 วัน ตามลำดับ จากการศึกษาได้สร้างแผนภาพระบบไทรภาคซึ่งประกอบด้วยไตรกลีเซอไรด์ กลีเซอรอลโมโนโอเลตและน้ำขึ้นและศึกษาโครงสร้างของวัสดุภาคผลึกเหลวโดยใช้กล้องจุลทรรศน์แสงพอลาไรซ์ จากการพิจารณาความสามารถเกิดผลึกเหลวแบบรีเวอร์สเฮกซาโกนาล จึงได้เลือกสูตรตำรับซึ่งประกอบด้วยไตรกลีเซอไรด์ : กลีเซอรอลโมโนโอเลต : น้ำเท่ากับ 6:15:79 เป็นระบบนำส่งยา จากการศึกษาการปลดปล่อยยาพบว่าไคโตซานไมโครสเฟียร์ที่บรรจุด็อกซีซัยคลินโดยใช้กลีเซอรอลโมโนโอเลตเป็นระบบนำส่งยาสามารถปลดปล่อยยาได้นาน 48 ชั่วโมงและเป็นไปตามจลนศาสตร์รากที่สองของเวลา นอกจากนี้ไคโตซานไมโครสเฟียร์ที่บรรจุด็อกซีซัยคลินไฮคลอเตโดยใช้กลีเซอรอลโมโนโอเลตเป็นระบบนำส่งยาสามารถออกฤทธิ์ต้านเชื้อในหลอดทดลองต่อเชื้อ *Staphylococcus aureus* ATCC 6538P ซึ่งเป็นเชื้อที่พบได้ในร่องเหงือกของผู้ป่วยโรคปริทันต์อักเสบ

ภาควิชา..... เภสัชกรรม..... ลายมือชื่อนิสิต..... *ชินษรฐา สิงห์วีรญุสนธรม์*
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KHANITTHA SINGHIRUNNUSORN: FORMULATION OF DOXYCYCLINE LOADED CHITOSAN MICROSPHERES IN GLYCERYL MONOOLEATE-BASED DRUG DELIVERY SYSTEMS FOR PERIODONTITIS. THESIS ADVISOR: ASSOC. PROF. SUCHADA CHUTIMAWORAPAN, Ph.D. THESIS COADVISOR: ASSOC. PROF. AREERAT LAORPAKSA, M. Sc. in PHARM 182 pp.

The purposes of this study were to develop chitosan microspheres containing doxycycline hyclate and incorporate into glyceryl monooleate-based drug delivery system for the treatment of periodontal disease. The chitosan microspheres were prepared by using emulsification and ionotropic gelation method. The Box-Behnken experimental design was used as a tool for optimize the formulation. From the result obtained the formulations comprising of doxycycline hyclate load (%), chitosan (%) and sodium tripolyphosphate (STPP) (%) as 75:3:15, 75:4:10 and 30:3:10 were selected. The microspheres could sustain release of doxycycline hyclate over a period of 24 hrs and followed square root of time kinetic which indicated that the rate of release was diffusion controlled. The accelerated stability study at 40, 50, 60 and 70°C and the Arrhenius plot indicated that the predicted shelf-lives of microsphere formulations comprising of doxycycline hyclate load (%), chitosan(%) and STPP (%) of 75:3:15, 75:4:10 and 30:3:10 were 47.04, 245.65 and 22208.38 days, respectively. The ternary phase diagram consisted of triglyceride: glyceryl monooleate: water was constructed and the structure of liquid crystalline phases was investigated by using polarized light microscopy. Regarding the ability to form the reverse hexagonal liquid crystalline phase, the formulation containing triglyceride: glyceryl monooleate: water of 6:15:79 was selected as the drug delivery system. The release study indicated that the chitosan microspheres incorporated in glyceryl monooleate-based drug delivery system could prolong the release of doxycycline hyclate over a period of 48 hr and also followed square root of time kinetic. Additionally, the doxycycline hyclate loaded chitosan microspheres in glyceryl monooleate-based drug delivery system exhibited *in vitro* antimicrobial activity against *Staphylococcus aureus* ATCC 6538P, which was found in the periodontal pockets of patients with periodontitis.

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LISTS OF ABBREVIATIONS

ANOVA	=	analysis of variance
C.V.	=	coefficient of variation
CC	=	chitosan concentration
CFU	=	colony-forming unit
cps	=	centipoises
°C	=	degree Celsius
DA	=	degree of acetylation
DC	=	doxycycline hyclate concentration
DD	=	degree of deacetylation
DSC	=	differential scanning calorimetry
GCF	=	gingival crevicular fluid
GMO	=	glyceryl monooleate
EVA	=	ethylene vinyl acetate
H _{II}	=	reversed hexagonal phase
HPLC	=	high performance liquid chromatography
hr	=	hour
k ₀	=	zero-order release rate constant
k ₁	=	first-order release rate constant
kg	=	kilogram
k _H	=	diffusion rate constant
LSD	=	least significant difference
L _α	=	lamellar phase
mg	=	milligram
MIC	=	minimum inhibitory concentration
min	=	minute
ml	=	milliliter
mm	=	millimeter
n	=	sample size
nm	=	nanometer
No.	=	number
PLGA	=	poly (lactide/glycolide)

PMN	=	polymorphonuclear
R ²	=	coefficient of determination
rpm	=	revolution per minute
SD	=	standard deviation
SEM	=	scanning electron microscope
SPSS	=	statistical package for the social science
STPPC	=	sodium tripolyphosphate concentration
SEM	=	scanning electron microscope
µg	=	microgram
UV	=	ultraviolet
v/v	=	volume by volume
w/v	=	weight by volume
w/w	=	weight by weight