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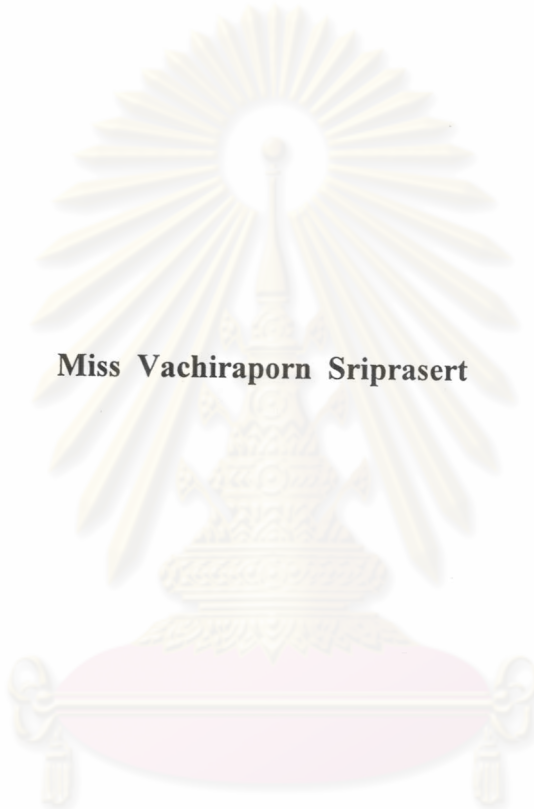
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ลิขสิทธิ์ของจุฬาลงกรณ์มหาวิทยาลัย

**DEVELOPMENT OF METRONIDAZOLE MICROEMULSION GEL
FOR PERIODONTAL USE**



Miss Vachiraporn Sriprasert

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for the Degree of Master of Sciences in Pharmacy in Industrial Pharmacy**

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สารที่ยอมรับทางเภสัชกรรมว่าปลอดภัยหลายชนิดได้ถูกนำมาศึกษาความเป็นไปได้ในการเกิดไมโครอิมัลชันเจล และระบบผลึกเหลว วิธีการเตรียมสามารถเกิดขึ้นได้เองโดยการผสมส่วนประกอบทั้งสี่ชนิดเข้าด้วยกัน คือ น้ำมัน, สารลดแรงตึงผิว, สารลดแรงตึงผิวร่วม โดยใช้ไฮโซโพรพิลเมอริสเตท, น้ำมันละหุ่ง และน้ำมันถั่วเหลืองเป็นส่วนของน้ำมัน และใช้ทวิน80, คลีโมฟอริอัล, คลีโมฟอริอาร์เอช40 เป็นสารลดแรงตึงผิว และใช้ลูทอรอลเอฟ-68, บrijf72, บrijf721-เอส, บrijf35, เซทิลแอลกอฮอล์, บิวทานอล, กลีเซอริน และ โพรพิลีนไกลคอลเป็นสารลดแรงตึงผิวร่วม และนำในการศึกษาครั้งนี้ จากนั้นทำการสร้างเฟสไดอะแกรมจากระบบที่เตรียมจากส่วนประกอบดังกล่าวเพื่อศึกษาพื้นที่การเกิดไมโครอิมัลชันเจลและระบบผลึกเหลว โดยใช้กล้องโพลาริไสต์ตรวจสอบการเกิดและกำหนดลักษณะโครงสร้างของไมโครอิมัลชันเจลและระบบผลึกเหลวที่เกิดขึ้น และยังใช้กล้องจุลทรรศน์อิเล็กตรอนควบคู่ไปกับการใช้โปรแกรมซีมาฟอร์ เพื่อศึกษาขนาดและการกระจายของอนุภาค นอกจากนี้ยังทำการศึกษาคุนสมบัติทางกายภาพเคมีของระบบ ทั้งก่อนและหลังการศึกษาความคงตัวของระบบรวมทั้ง การสังเกตด้วยตา, ชนิดของไมโครอิมัลชันเจล, คุณสมบัติการนำไฟฟ้า, พีเอช, การไหลผ่านเข็มฉีดยา, ความหนืด และความสามารถในการละลายตัวยากฤทธิ์ของไมโครอิมัลชันเจลและระบบผลึกเหลวที่เตรียมได้ ในการประเมินความเป็นไปได้ในการใช้ไมโครอิมัลชันเจลและระบบผลึกเหลวเพื่อควบคุมการปลดปล่อยของมาโรนิตาโซล 1.5% โดยน้ำหนักโดยใช้ฟรานซ์ดีฟฟิวชันเซลล์ รวมทั้งการประเมินความเป็นไปได้ในการเป็นระบบนำส่งยาที่ใช้ในร่องเหงือกด้วยการศึกษาประสิทธิภาพในการต้านเชื้อจุลชีพที่มีต่อเชื้อพอไฟโรโมนาส จิงจิวอลลิส ของระบบไมโครอิมัลชันเจลและระบบผลึกเหลวที่เตรียมได้

จากการศึกษาพบว่าชนิดและอัตราส่วนของสารลดแรงตึงผิว, สารลดแรงตึงผิวร่วม และน้ำมันมีผลต่อพื้นที่ในการเกิดไมโครอิมัลชันเจลและระบบผลึกเหลว ซึ่งไมโครอิมัลชันเจลสามารถเกิดขึ้นได้เมื่อมีชนิดและอัตราส่วนขององค์ประกอบที่เหมาะสมและเกิดได้ในพื้นที่จำกัด จากผลการทดลองพบว่าการใช้บิวทานอล, เซทิลแอลกอฮอล์, บrijf 72 และกลีเซอรินเป็นสารลดแรงตึงผิวร่วม ไม่สามารถทำให้เกิดไมโครอิมัลชันเจลและระบบผลึกเหลวได้ พบว่าพื้นที่ในการเกิดไมโครอิมัลชันเจลในเฟสไดอะแกรมเพิ่มขึ้นเมื่ออัตราส่วนของน้ำมันต่อสารลดแรงตึงผิวลดลง ผลการทดสอบโดยการเจาะจง, การย้อมสี รวมทั้งการทดสอบการนำไฟฟ้าพบว่าระบบที่ศึกษาส่วนใหญ่เกิดไมโครอิมัลชันชนิดน้ำมันในน้ำ ขนาดอนุภาคจากกล้องจุลทรรศน์อิเล็กตรอนพบว่าขนาดของอนุภาคอยู่ในช่วง 25-85 นาโนเมตร และขนาดเส้นผ่านศูนย์กลางเฉลี่ยของไมโครอิมัลชันเจลเพิ่มขึ้นภายหลังการทดสอบความคงตัว ชนิดและอัตราส่วนขององค์ประกอบในตำรับมีผลต่อความหนืดของไมโครอิมัลชันเจลและระบบผลึกเหลวที่ได้ การประเมินความเป็นไปได้ในการใช้ไมโครอิมัลชันเจลและระบบผลึกเหลว เป็นระบบนำส่งยาที่ใช้ในร่องเหงือก แสดงให้เห็นว่าระบบสามารถที่จะละลายตัวยาโรนิตาโซลได้ 1.5% โดยน้ำหนัก นอกจากนี้ยังพบว่าระบบที่ได้ส่วนใหญ่มีการกระจายแสงภายใต้กล้องโพลาริไสต์ ควบคู่ไปกับคุณสมบัติการไหลแบบนอนนิวโตเนียน และเชียวทินนิ่ง ซึ่งคุณสมบัติดังกล่าวทำให้ระบบที่ได้มีคุณสมบัติการไหลผ่านเข็มฉีดยาที่ดีและง่ายต่อการฉีดเฉพาะที่ จากคุณสมบัติการปลดปล่อยตัวยาก พบว่าทุกระบบสามารถควบคุมการปลดปล่อยตัวยากได้ยาวนานกว่า 24 ชั่วโมง โดยมีจลนศาสตร์การปลดปล่อยตัวยากเป็นแบบฮิกูชิ และจลนศาสตร์อันดับหนึ่ง สำหรับประสิทธิภาพในการต้านเชื้อจุลชีพในช่องปากของระบบที่ได้พบว่าสามารถแสดงเส้นผ่านศูนย์กลางของขอบเขตในการยับยั้งเชื้อ พอไฟโรโมนาส จิงจิวอลลิส โดยวิธีการดีฟฟิวชัน ภายหลังการทดสอบความคงตัวภายใต้สภาวะแรงและภายหลังจากการเก็บที่อุณหภูมิ 45 องศาเซลเซียสเป็นระยะเวลา 4 เดือน พบว่าไมโครอิมัลชันเจลและระบบผลึกเหลวที่มีความคงตัวทั้งทางกายภาพและเคมี

ภาควิชา.....เภสัชอุตสาหกรรม.....ลายมือชื่อนิสิต.....*วชิรพร ศรีประเสริฐ*
สาขาวิชา.....เภสัชอุตสาหกรรม.....ลายมือชื่ออาจารย์ที่ปรึกษา.....*ผอ. พิ*
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KEY WORD: METRONIDAZOLE / MICROEMULSION GEL / LIQUID CRYSTAL / PHYSICO-CHEMICAL PROPERTY / BIREFRINGENT PROPERTY / SYRINGEABILITY / VISCOSITY / ANTIMICROBIAL ACTIVITY / *PORPHYROMONAS GINGIVALIS* / PERIODONTAL DRUG DELIVERY

VACHIRAPORN SRIPRASERT: THESIS TITLE. (DEVELOPMENT OF METRONIDAZOLE MICROEMULSION GEL FOR PERIODONTAL USE)
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Various pharmaceutically acceptable components were investigated the possibility to form microemulsion gel (MEG) and liquid crystal (LC). Spontaneous formation was obtained by mixing four components. Isopropyl myristate (IPM), castor oil (CO) and soybean oil (SBO) were used as an oil phase; tween 80 (T_{80}), cremophor EL (C_{EL}) and cremophor RH (C_{RH}) as surfactant; Lutrol F-68 (L_{68}), Brij 72 (B_{72}), Brij 721S (B_{721s}), Brij 35 (B_{35}), cetyl alcohol (C), butanol (B), glycerin (G) and propylene glycol (PG) as cosurfactant and ultrapure water were used. Pseudo-ternary phase diagrams were constructed from various combinations of these excipients to evaluate the MEG and LC existing area. Polarized light microscope was used to elucidate the formation, structure and microscopic pattern of the obtained MEG and LC. Transmission electron microscope (TEM) and *SemAfore* computerized program were used to determine the particle size and size distribution of system. The physicochemical properties were also investigated both before and after stability testing including visual observation, MEG type, conductivity, pH, syringeability, viscosity, loading capacity of selected MEG and LC. The potential of MEG and LC to prolong the release of 1.5% w/w metronidazole was accordingly evaluated *in vitro* using modified Franz diffusion cell whereas the possibility to use MEG and LC as periodontal drug delivery was studied on the antimicrobial activity against *Porphyromonas gingivalis*.

The results indicated that types and ratios of surfactant, cosurfactant and oil used had pronounced effect on the existing region of MEG and LC. MEG area could be produced by specific type and ratio of component in a narrow range. B, C, B_{72} and G as cosurfactant could not form MEG at any ratio. The areas of MEG in pseudo-ternary phase diagrams were mostly increased with the decreasing oil to surfactant ratio. The results from dilution test and dye solubility test including conductivity test confirmed that most MEG and LC were o/w type. Results from TEM revealed that the mean droplet diameters of the system were in the range of 25-85 nm and increased after freeze-thawing. The type and amount of oil, surfactant and cosurfactant also affected the viscosity of system. Furthermore, the assessment of the possibility of using these systems as periodontal drug delivery showed that selected formulations could hold a maximum of 1.5% w/w metronidazole. Most systems exhibited birefringent property under cross-polarizing microscope. The non-newtonian and shear-thinning flow behaviors could be obtained indicating the good syringeability and injectability of the systems. The drug diffusion from MEG and LC systems was sustained to more than 24 hours and was best fitted with first order kinetic and Higuchi model. Antimicrobial activity of selected formulation showed the strong inhibition zone against *P. gingivalis*. by agar diffusion method. After accelerated and Thai FDA stability testing, MEG and LC still showed good physicochemical stability.

Department....Manufacturing Pharmacy.....Student's signature.....
 Field of study....Industrial Pharmacy.....Advisor's signature.....
 Academic year.....2003..... Co-advisor's signature.....

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จุฬาลงกรณ์มหาวิทยาลัย

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LIST OF ABBREVIATIONS

B	=	butanol
BBL	=	Trypticase soy agar
B35	=	Brij 35
B72	=	Brij 72
B721S	=	Brij 721S
C	=	cetyl alcohol
C _{EL}	=	cremophor EL
C _{RH}	=	cremophor RH40
CO	=	castor oil
°C	=	degree celcius (centigrade)
CPP	=	the critical packing parameter
cps	=	centipoise
E	=	emulsifier
EPO	=	Early Onset Periodontitis
et al.	=	et alii (and others)
FDA	=	Food and Drug Administration
FFA	=	free fatty acid
g	=	gram (s)
G	=	Glycerin
GCF	=	gingival crevicular fluid
HEC	=	hydroxy ethyl cellulose
HLB	=	hydrophile-lipophile balance
HPLC	=	High Performance Liquid Chromatography
hr	=	hour (s)
i. e.	=	id est (that is)
IPM	=	isopropyl myristate
IV	=	intravenous
LC	=	liquid crystal
Log	=	logarithm
L ₆₈	=	Lutrol F-68
L ₁₂₇	=	Lutrol F-127

LIST OF ABBREVIATIONS (Cont.)

MEG	=	microemulsion gel
MTZ	=	metronidazole
mg	=	milligram (s)
ml	=	milliliter (s)
mm	=	millimeter (s)
nm	=	nanometer (s)
NCCLS	=	National Committee for Clinical Laboratories Standard Procedure
NMR	=	nuclear magnetic resonance
No.	=	number of sample
o/w	=	oil in water
<i>Pg</i>	=	<i>Porphyromonas gingivalis</i>
PEG	=	polyethylene glycol
PG	=	propylene glycol
pH	=	the negative logarithm of the hydrogen ion concentration
PK_a	=	the negative logarithm of its acid dissociation constant
R^2	=	coefficient of determination
rpm	=	revolution per minutes
SANS	=	small angle x-ray neutron scattering
SBO	=	soybean oil
SD	=	standard deviation
T_{80}	=	tween 80
TEM	=	transmission electron microscopy
TOW	=	transparent oil in water microemulsion
UV	=	ultraviolet
v/v	=	volume by volume
W	=	water
w/o	=	water in oil
w/w	=	weight by weight
μg	=	microgram (s)
μL	=	microliter (s)
μm	=	micrometer (s)

LIST OF ABBREVIATIONS (Cont.)

- μS = microsemens
 λ_{max} = wavelength of maximum absorption



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