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EFFECT OF COSURFACTANTS ON THE PREPARATION OF INTRAVENOUS LIPID EMULSIONS

Miss Thanaphan Sakulchaijaroen

A Thesis Submitted in Partial Fulfillment of the Requirements
for the Degree of Master of Science Program in Pharmaceutical Technology

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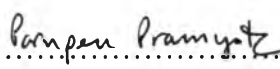
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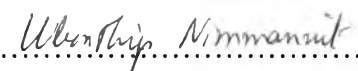
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By Miss Thanaphan Sakulchaijaroen
Field of Study Pharmaceutical Technology
Thesis Advisor Assistant Professor Warangkana Warisnoicharoen, Ph.D.
Thesis Co-advisor Pongsakornpat Arunothayanun, Ph.D.

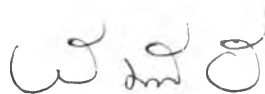
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Pharmaceutical Sciences
(Associate Professor Pornpen Pramyothin, Ph.D.)


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..... Chairman
(Associate Professor Ubonthip Nimmannit, Ph.D.)


..... Thesis Advisor
(Assistant Professor Warangkana Warisnoicharoen, Ph.D.)


..... Thesis Co-Advisor
(Pongsakornpat Arunothayanun, Ph.D.)


..... Member
(Pornchai Rojsitthisak, Ph.D.)


..... Member
(Suchat Watnasirichaikul, Ph.D.)

ธนพรรณ สกุลชัยเจริญ: ผลของสารลดแรงตึงผิวร่วมต่อการเตรียมอิมัลชันไขมันเพื่อให้ทางหลอดเลือดดำ (EFFECT OF COSURFACTANTS ON THE PREPARATION OF INTRAVENOUS LIPID EMULSIONS) อ.ที่ปรึกษา: ผศ.ดร. วรางคณา วาริสน้อยเจริญ, อ.ที่ปรึกษาร่วม: ดร. พงศกรพัฒน์ อรุโณทยานันท์, 175 หน้า. ISBN 974-14-2447-7

ความคงตัวของอิมัลชันไขมันเพื่อให้ทางหลอดเลือดดำเป็นสิ่งสำคัญสำหรับผู้ป่วยที่ต้องการอาหารทางหลอดเลือด จึงมีแนวคิดที่จะนำสารลดแรงตึงผิวมาใช้เพื่อปรับปรุงความคงตัวของอิมัลชันให้ดีขึ้น ในการเตรียมอิมัลชัน ไขมันที่ใช้คือน้ำมันถั่วเหลืองในความเข้มข้นร้อยละ 10 และ 20 สารก่ออิมัลชันที่ใช้ได้แก่ฟอสโฟลิปิดจากไข่ (ไลโปย อี80) เพียงชนิดเดียวหรือใช้ร่วมกันระหว่างฟอสโฟลิปิดจากไข่และสารลดแรงตึงผิวร่วมซึ่งได้แก่ทวิน 80 วิตามินอีที่พีจีเอสและโซเดียมโอเลต ในขั้นตอนการเตรียมได้มีการปรับเปลี่ยนตัวแปรที่มีผลต่ออิมัลชันอันได้แก่ เวลาในการปั่นผสมด้วยเครื่องปั่นผสมความเร็วสูง ความดันและจำนวนรอบในการผ่านสารเข้าสู่เครื่องปั่นผสมชนิดความดันสูง จากนั้นนำตัวรับที่เตรียมได้ไปผ่านกระบวนการทำให้ปราศจากเชื้อโดยใช้หม้อนึ่งอัดไอและตรวจสอบคุณสมบัติทางเคมีกายภาพ ผลการศึกษาพบว่าตัวรับที่ประกอบด้วยฟอสโฟลิปิดจากไข่ผสมกับวิตามินอีที่พีจีเอส และฟอสโฟลิปิดจากไข่ผสมกับทวิน 80 สามารถเตรียมอิมัลชันไขมันที่คงตัวได้ อิมัลชันไขมันที่ประกอบด้วยน้ำมันถั่วเหลืองร้อยละ 10 ฟอสโฟลิปิดจากไข่ร้อยละ 1 และวิตามินอีที่พีจีเอสร้อยละ 0.5 เป็นตัวรับที่เหมาะสมเนื่องจากใช้สารก่ออิมัลชันในปริมาณต่ำ และมีคุณสมบัติทางเคมีกายภาพตามข้อกำหนดของผลิตภัณฑ์เพื่อให้ทางหลอดเลือดดำ โดยอิมัลชันที่เก็บที่อุณหภูมิห้องและในสภาวะเร่ง (4°C และ 40°C) มีความคงตัวนานถึง 4 สัปดาห์ ขนาดอนุภาคก่อนและหลังผ่านหม้อนึ่งอัดไอมีค่า 0.201 และ 0.199 ไมโครเมตร ตามลำดับ หลังจากเก็บไว้เป็นเวลา 24 ชั่วโมง ค่าความเป็นกรด-ด่าง ค่าออสโมแลลลิตี และค่าความต่างศักย์ที่ผิวอนุภาคของอิมัลชันที่ผ่านหม้อนึ่งอัดไอมีค่า 6.97, 324 มิลลิออสโมลต่อกิโลกรัม และ -41.77 มิลลิโวลต์ ตามลำดับ ค่าความเป็นกรด-ด่างมีค่าลดลงเล็กน้อย ในขณะที่ค่าความต่างศักย์ที่ผิวอนุภาคมีค่าสูงขึ้นเมื่อเก็บไว้ในทุกสภาวะที่ศึกษา นอกจากนี้พบว่าเมื่อใช้ทวิน 80 แทนวิตามินอีที่พีจีเอส อนุภาคของอิมัลชันที่ได้มีขนาดใหญ่ขึ้นเล็กน้อย อย่างไรก็ตามตัวรับที่ได้มีความคงตัวได้นานถึง 4 สัปดาห์ เมื่อเก็บที่อุณหภูมิห้อง กล่าวโดยสรุปปัจจัยที่เกี่ยวข้องในการเตรียมอิมัลชันได้แก่ ขบวนการผ่านสารเข้าสู่เครื่องปั่นผสม และความคงตัวหลังผ่านความร้อน รวมถึงชนิดและปริมาณของสารลดแรงตึงผิวที่ใช้ สารลดแรงตึงผิวร่วมชนิดไม่มีประจุสามารถเพิ่มความคงตัวของอิมัลชันหลังกระบวนการทำให้ปราศจากเชื้อด้วยหม้อนึ่งอัดไอและเก็บไว้ได้นานถึง 4 สัปดาห์ โดยใช้หลักการที่ทำให้คงตัวด้วยแรงสเตอร์ริกของสายพอลิเมอร์ของสารลดแรงตึงผิว

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ปีการศึกษา 2548.....

ลายมือชื่อนิสิต *ธนพรรณ สกุลชัยเจริญ*

ลายมือชื่ออาจารย์ที่ปรึกษา *ดร. พงศกรพัฒน์ อรุโณทยานันท์*

ลายมือชื่ออาจารย์ที่ปรึกษาร่วม *ดร. วรางคณา วาริสน้อยเจริญ*

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PHYSICOCHEMICAL PROPERTIES

THANAPHAN SAKULCHAIJAROEN: EFFECT OF COSURFACTANTS ON THE PREPARATION OF INTRAVENOUS LIPID EMULSIONS. THESIS ADVISOR: ASSIST. PROF. WARANGKANA WARISNOICHAROEN, Ph.D., THESIS COADVISOR: PONGSAKORNPAT ARUNOTHAYANUN, Ph.D. 175 p.p. ISBN 974-14-2447-7

The stability of intravenous lipid emulsions is important for patients requiring parenteral nutrition. The use of cosurfactant is thought to improve the emulsion stability. For the emulsion preparation, the oil used were 10% and 20% soybean oil, the emulsifier were used either egg phospholipids (Lipoid® E80) alone or combined with a cosurfactant, Tween® 80, Vitamin E-TPGS or sodium oleate. The methods of preparation were varied in homogenization time, pressure and cycles through high pressure homogenizer. The formulations were sterilized by autoclaving and the physicochemical properties were investigated. The results illustrated that the formulations composed of a combination of egg phospholipids with either Vitamin E-TPGS or Tween® 80 could form the stable emulsions. The lipid emulsion containing 10% soybean oil emulsified by 1.0% egg phospholipids and 0.5% Vitamin E-TPGS was suggested due to low amount of emulsifier used and proper physicochemical properties complied with parenteral product requirements. The emulsion could remain stable for 4 weeks both at room temperature and in accelerate condition (4°C and 40°C). Its particle size (D[4,3]) of such formulation before and after autoclaving were 0.201 and 0.199 µm, respectively. The pH, osmolality and the value of zeta potential of the autoclaved emulsion after 24 hours were 6.97, 324 mOsm/kg and -41.77 mV, respectively. The pH was slightly decreased during storage while the zeta potential was increased as a function of time in all conditions. When Tween® 80 replaced Vitamin E-TPGS, the slightly larger in particle size of emulsion was observed, however the formulation still remained stable up to 4 weeks after storage at room temperature. It was concluded that the factors involved in the emulsion preparation were the process of homogenization, heat stabilization as well as the type and amount of surfactants used. The nonionic cosurfactant could improve the formation of emulsion which was stable after autoclaving and storage for at least 4 weeks by possibly the steric stabilization of the polymeric surfactant layer.

Field of study ...Pharmaceutical Technology...

Academic year2005.....

Student's signature*Thanaphan S*.....

Advisor's signature*Warangkana Warisnoicharoen*.....

Co-advisor's signature*Pongsakornpat Arunothayanun*.....

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LIST OF ABBREVIATIONS

BHA	Butylatedhydroxyl anisole
BHT	Butylatedhydroxyl toluene
EPC	Egg phospholipids
<i>et al.</i>	et alli (and others)
FFA	Free fatty acid
HLB	Hydrophile-lipophilic balance
i.e.	id est (that is)
kPa	Kilo pascal
LCT	Long chain triglycerides
Lot no.	Lot number
LPC	Lysophosphatidylcholine
LPE	Lysophosphatidylethanolamine
MCT	Medium chain triglycerides
mg	milligram
mL	milliter
mmHg	millimeter of mercury
mOsm/kg	milliosmol per kilogram
mOsm/L	milliosmol per liter
mV	millivolt
N	normality
ND	not determined

nm	nanometer
o/w	oil-in-water
PA	Phosphatidic acid
PC	Phosphatidylcholine
PE	Phosphatidylethanolamine
PFEs	Parenteral fat emulsions
PI	Phosphatidylinositol
PL	Phospholipid
PS	Phosphatidylserine
psi	pound (s) per square inch
w/o	water-in-oil
w/w	weight by weight
μm	micrometer