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**PARTITION BEHAVIOR OF LIPOPHILIC COMPOUNDS INCORPORATED
IN SUBMICRON EMULSION: EFFECTS OF PHYSICOCHEMICAL
PROPERTIES, CONCENTRATIONS AND INCORPORATION METHODS**

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การศึกษาผลของคุณสมบัติทางเคมีกายภาพ ความเข้มข้นและวิธีการแทรกผสมต่อการกระจายตัวของสารทางเภสัชกรรมไปสู่ภูมิภาคต่าง ๆ ในอิมัลชันที่มีอนุภาคขนาดซับไมครอน โดยใช้สารในกลุ่มของอัลคิล-4-ไฮดรอกซีเบนโซเอท ได้แก่ เมธิลพาราเบน เอธิลพาราเบน โพรพิลพาราเบน และบิวทิลพาราเบน และตัวยานในกลุ่มของเบนโซโอะซีพิน ได้แก่ อัลทราโซแลม โคลนาซีแพม ไดอะซีแพม และลอร์อาซีแพม เป็นสาร/ตัวยาดันแบบในการศึกษานี้ โดยที่ค่าการละลายในน้ำ ค่าการละลายในน้ำมัน และค่าสัมประสิทธิ์การกระจายระหว่างน้ำมันและน้ำของสารในกลุ่มอัลคิล-4-ไฮดรอกซีเบนโซเอทมีความสัมพันธ์กับโครงสร้างทางเคมี ขณะที่ไม่พบความสัมพันธ์ดังกล่าวในกลุ่มของเบนโซโอะซีพิน ทำการแทรกผสมสาร/ตัวยานอิมัลชันที่มีขนาดซับไมครอน 3 วิธี ได้แก่ การแทรกผสมโดยละลายสาร/ตัวยานในภูมิภาคน้ำมันก่อนนำไปผ่านขบวนการอิมัลซิฟิเคชัน (de novo emulsification) การละลายสาร/ตัวยานในตัวทำละลายก่อนนำไปผสมกับอิมัลชันพื้นที่ไม่มียา (extemporaneous addition) และการปั่นผสมผงของสาร/ตัวยานในอิมัลชันพื้นที่ไม่มียา (shaking method) จากการทดลองพบว่าอิมัลชันที่มีสาร/ตัวยานแทรกผสมอยู่มีขนาดใหญ่ขึ้น ประจุที่พื้นผิวของอนุภาคและความเป็นกรด-เบสมีค่าลดลงเมื่อเปรียบเทียบกับอิมัลชันพื้นที่ไม่มียาและเมื่อเก็บไว้ที่อุณหภูมิห้องในระยะเวลา 7 วัน อนุภาคของอิมัลชันของทั้งที่มีและไม่มีสาร/ตัวยานแทรกผสมอยู่มีขนาดใหญ่ขึ้น ขณะที่ประจุที่พื้นผิวของอนุภาคมีปริมาณมากขึ้นและความเป็นกรด-เบสมีค่าลดลง ใช้เทคนิคการปั่นเหวี่ยงความเร็วสูงเพื่อแยกอิมัลชันออกเป็น 4 ภูมิภาค ประกอบด้วย ภูมิภาคน้ำมัน ชั้นของฟอสโฟลิปิด ภูมิภาคน้ำและเมโซเฟสแล้วทำการวิเคราะห์หาปริมาณสารตัวอย่างในแต่ละภูมิภาค การทดลองพบว่าสาร/ตัวยานที่ชอบไขมันมากจะสะสมอยู่ในภูมิภาคน้ำมัน สาร/ตัวยานที่ชอบไขมันปานกลางมักจะกระจายตัวไปยังชั้นของฟอสโฟลิปิดและเมโซเฟส ส่วนสาร/ตัวยานที่ชอบไขมันน้อยมักจะกระจายอยู่ในภูมิภาคน้ำ อย่างไรก็ตามความเข้มข้นของสาร/ตัวยานที่แทรกผสมไม่มีผลอย่างเด่นชัดต่อการกระจายตัวของสาร/ตัวยานในแต่ละภูมิภาคของอิมัลชันที่มีอนุภาคขนาดซับไมครอน นอกจากนี้วิธีการแทรกผสมมีผลต่อการกระจายตัวของสาร/ตัวยานในอิมัลชันที่มีอนุภาคขนาดซับไมครอนซึ่งขึ้นอยู่กับว่าภูมิภาคใดสัมผัสกับสาร/ตัวยานเป็นลำดับแรก จากการทดลองพบว่าสาร/ตัวยานที่แทรกผสมในอิมัลชันที่มีอนุภาคขนาดซับไมครอนโดยวิธีการละลายตัวยานในภูมิภาคน้ำมันก่อนนำไปผ่านขบวนการอิมัลซิฟิเคชันส่วนใหญ่จะสะสมอยู่ในภูมิภาคน้ำมัน และกระจายอยู่ในภูมิภาคน้ำและเมโซเฟสเป็นส่วนใหญ่เมื่อแทรกผสมโดยวิธีละลายสาร/ตัวยานในตัวทำละลายก่อนนำไปผสมหรือปั่นผสมผงกับอิมัลชันพื้นที่ไม่มียา

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สาขาวิชา เภสัชกรรม

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WARISADA SILA-ON: PARTITION BEHAVIOUR OF LIPOPHILIC COMPOUNDS INCORPORATED IN SUBMICRON EMULSION: EFFECTS OF PHYSICOCHEMICAL PROPERTIES, CONCENTRATIONS AND INCORPORATION METHODS. THESIS ADVISOR: ASSOCIATE PROFESSOR POJ KULVANICH, Ph.D., THESIS CO-ADVISOR: ASSISTANT PROFESSOR BOONSRI ONGPIPATTANAKUL, Ph.D., NONTIMA VARDHANABHUTI, Ph.D., 265 pp. ISBN 974-17-5125-7

The effects of physicochemical properties, concentration and method of incorporation of pharmaceutical substances on their partitions in various phases of submicron emulsion were studied. Series of alkyl-4-hydroxybenzoate comprising methylparaben, ethylparaben, propylparaben and butylparaben, and series of benzodiazepine drugs comprising alprazolam, clonazepam, diazepam and lorazepam, were used as model substances. Determination of aqueous solubility, oil solubility and oil-water partition coefficient indicated the relationship of these parameters with molecular structure of alkyl-4-hydroxybenzoate group whereas no correlation with chemical structure of benzodiazepine drugs was observed. Three methods of drug incorporation were investigated, dissolved model compound in oil phase prior to emulsification process (de novo emulsification), the model compound was dissolved in solubilizer and then mixed with submicron emulsion base (extemporaneous addition) and directly shaking of drug powder in submicron emulsion base (shaking method). The larger mean particle size and the lower in zeta potential including pH value of drug containing emulsion were observed as compared with submicron emulsion bases. After keeping at ambient temperature for a period of seven days, the mean particle size was larger while the higher zeta potential and lower pH were observed in drug containing submicron emulsions as well as submicron emulsion bases. Ultracentrifugation technique was used to separate emulsion into different phases namely oil phase, phospholipids rich phase, aqueous phase and mesophase, then drug content in each phase was determined. The higher lipophilic model substance was mostly deposited in oil phase. The moderate lipophilic drug likely partitioned to the phospholipids rich phase and mesophase. The lower lipophilic drug predominantly distributed to the aqueous phase. However, the concentration of incorporated drug apparently had less effect on the distribution through various phases of submicron emulsion. In addition, method of incorporation affected the distribution of model substance in submicron emulsion depending on which phase that was firstly contacted with the incorporated drug molecule. Drug incorporating in submicron emulsion by de novo emulsification mostly accumulated in oil phase, whereas was predominantly accumulated in aqueous phase and mesophase when incorporating by extemporaneous addition and shaking method, respectively.

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LIST OF ABBREVIATIONS

° C	:	degree celcius
µm	:	micrometre
aq.	:	aqueous
cm	:	centimetre
DMA	:	dimethylacetamide
DMSO	:	dimethylsulfoxide
g	:	gram
HPLC	:	High Performance Liquid Chromatrography
hr	:	hour
LCT	:	long chain triglyceride
LD	:	Laser Diffraction
Log P _{o/w}	:	oil-water partition coefficient
MCT	:	medium chain triglyceride
mg	:	milligram
ml	:	millilitre
mV	:	millivolt
nm	:	nanometre
O/W	:	oil in water
O/W/O	:	oil in water in oil
PC	:	phosphatidylcholine

LIST OF ABBREVIATIONS (Continued)

PCS	:	Photon Correlation Spectroscopy
PG	:	phosphatidylglycerol
PI	:	polydispersity index
r	:	correlation
R ²	:	coefficient of determination
SD	:	standard deviation
SLN	:	solid lipid nanoparticle
SPE	:	solid phase extraction
W/O	:	water in oil
W/O/W	:	water in oil in water



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