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SOLID LIPID NANOPARTICLES AS COLLOIDAL DRUG CARRIERS FOR PARENTERAL ADMINISTRATION : STUDY ON PREPARATION PARAMETERS AND THEIR PHYSICOCHEMICAL CHARACTERISTICS

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การวิจัยนี้เป็นการศึกษาการเตรียมนาโนพาร์ทิเคิลของไขมันแข็งสำหรับใช้ในยาฉีดโดยวิธีการโฮโมจีไนเซชันที่อุณหภูมิสูง และทำการประเมินพารามิเตอร์ของกระบวนการเตรียม เพื่อให้ได้อนุภาคที่มีขนาดเล็กที่สุดโดยใช้พลังงานในการเตรียมน้อยที่สุด การศึกษานี้ใช้สารไขมันแข็ง 4 ชนิด คือ ไตรไมริสติน, ไตรปาลมิติน, ไตรสเตียริน, และกรดสเตียริก และมีสารเพิ่มความคงตัว 3 ชนิด ได้แก่ พอลอกซาเมอร์ 407, ทวีน 80, และเลซิทินจากไข่แดง โดยมีการใส่ยา 4 ชนิดที่มีคุณสมบัติในด้านการละลายต่างกันเข้าในตำรับ คือ ดิลไทอะเซม ไฮโดรคลอไรด์, ทีโอฟิลลีน, ไพรอกซิแคม, และไอบูโพรเฟน แล้วทำให้ตำรับปราศจากเชื้อและทำการศึกษาคุณสมบัติทางเคมีกายภาพของตำรับ จากผลการทดลองพบว่าพอลอกซาเมอร์ 407 ในความเข้มข้น 3% เป็นสารเพิ่มความคงตัวที่สามารถทำให้ไตรปาลมิติน 5% มีขนาดอนุภาคเล็กที่สุดในช่วงนาโนเมตร เส้นผ่าศูนย์กลางของ50%ของอนุภาคโดยปริมาตร ก่อนและหลังทำไร้เชื้อมีขนาด 0.39 และ 0.40 ไมโครเมตร ตามลำดับ และมีขนาดคงเดิมหลังจากเก็บไว้เป็นเวลามากกว่า 1 ปี แม้ว่าตำรับนี้จะมีค่าความหนืดต่ำ มีประจุที่ผิวของอนุภาคไม่เพียงพอที่จะทำให้ตำรับคงตัวได้โดยกลไกการผลักกันของประจุ แต่ตำรับนี้สามารถคงตัวได้โดยมีกลไกของความระเกะระกะของพอลอกซาเมอร์ 407 เสริมด้วย พบว่าสามารถเตรียมตำรับที่มีการใส่ตัวยาดิลไทอะเซม ไฮโดรคลอไรด์, ทีโอฟิลลีน และ ไอบูโพรเฟน ในนาโนพาร์ทิเคิลของไขมันแข็ง แต่ไม่สามารถเตรียมได้สำหรับยาไพรอกซิแคม โดยพบว่าเกิดการตกตะกอนของตัวยา และจากการตรวจสอบโดยเทคนิคอินฟราเรดสเปกโตรสโคปีพบว่าเกิดความไม่เข้ากันระหว่างตัวยากับสารไขมัน ประสิทธิผลของยาที่เข้าไปอยู่ในแมทริกซ์ของไขมันแข็งของไอบูโพรเฟนสูงกว่ายาอีก 2 ชนิด อย่างไรก็ตาม สามารถปรับปรุงประสิทธิผลของยาที่เข้าไปอยู่ในแมทริกซ์ของไขมันแข็งของดิลไทอะเซม ไฮโดรคลอไรด์ได้โดยการเพิ่มพีเอชของตำรับให้ใกล้เคียงกับค่าพีเอชของการแตกตัวของยา ซึ่งทำให้ยาอยู่ในรูปที่ไม่แตกตัวเพิ่มขึ้น และมีความชอบไขมันเพิ่มขึ้น ดิลไทอะเซม ไฮโดรคลอไรด์ และไอบูโพรเฟนในนาโนพาร์ทิเคิลของไขมันแข็งสามารถปลดปล่อยตัวยาได้นานกว่า 24 ชั่วโมง และ 7 วัน ตามลำดับ กลไกการปลดปล่อยตัวยาเป็นไปตามจลนศาสตร์ของการแพร่ผ่านแมทริกซ์ของฮิกูชิและจลนศาสตร์ของสมการกำลัง ผลของดิฟเฟอเรนเชียลสแกนนิงคาลอริเมทรี และเอกซเรย์ดิฟแฟรกโตเมทรีแสดงให้เห็นว่าตัวยาที่อยู่ในสารไขมันแข็งไม่ได้เป็นรูปผลึก ระบบตัวพานี้สามารถเตรียมซ้ำได้และมีคุณสมบัติเหมือนเดิมทุกครั้ง

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WIWAT PICHAYAKORN : SOLID LIPID NANOPARTICLES AS COLLOIDAL DRUG CARRIERS FOR PARENTERAL ADMINISTRATION : STUDY ON PREPARATION PARAMETERS AND THEIR PHYSICOCHEMICAL CHARACTERISTICS. THESIS ADVISOR : ASSOC. PROF. GARNPIMOL C. RITTHIDEJ, Ph.D. 324 pp. ISBN 974-332-896-3.

Solid lipid nanoparticles (SLN) for parenteral administration was produced by hot melt homogenization technique. The effects of homogenization parameters were studied and optimized to yield the smallest particle size and to use the least energy. Trimyristin, tripalmitin, tristearin, and stearic acid were used as lipid matrices, and their stabilizers were poloxamer 407, tween 80 and egg lecithin. Four drugs with different solubilities: diltiazem hydrochloride, theophylline, piroxicam, and ibuprofen were loaded into these carriers. The preparations were sterilized and their physicochemical characteristics were investigated. The results showed that 3% poloxamer 407 could stabilize 5% tripalmitin giving the smallest particles in nanometer size range. Its d(v,0.5) was 0.39 μm and 0.40 μm before and after autoclaving, respectively, and maintained in this size range for more than 1 year. Its viscosity was very low. The zeta potential was not sufficiently high to stabilize the dispersion solely by electrostatic repulsive, however, additional steric effect of poloxamer 407 could result in the stable dispersion. Diltiazem hydrochloride, theophylline, and ibuprofen loaded SLN could be prepared into stable preparations, which was not the case of piroxicam. Precipitation of drug occurred and incompatibility of piroxicam and tripalmitin was confirmed from the infrared spectra. Entrapment efficiency of ibuprofen in tripalmitin was higher than that of the other drugs. However, the higher entrapment efficiency of diltiazem hydrochloride could be improved by increasing the pH of the preparation nearly to its pKa, therefore its non-ionized form and lipophilicity were increased. The release profiles of diltiazem hydrochloride and ibuprofen SLN could be sustained for more than 24 hours and 7 days, respectively. Their release kinetics followed Higuchi and power expression models. DSC thermograms and X-ray diffractograms indicated that drug in lipid matrix was not in crystalline form. These carrier systems could be reproduced to have the similar properties in each batch.

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LIST OF ABBREVIATIONS

CV	=	coefficient of variation
°C	=	degree celcius
d(4,3)	=	the volume weighted mean diameter
d(3,2)	=	the surface weighted mean diameter
d(v,0.1)	=	the diameter of particles of 10% volume percentile
d(v,0.5)	=	the diameter of particles of 50% volume percentile
d(v,0.9)	=	the diameter of particles of 90% volume percentile
DSC	=	differential scanning calorimetry
e.g.	=	exampli gratia (for example)
EL	=	egg lecithin
et al.	=	et alii (and others)
etc.	=	et cetera (and so on)
FT-IR	=	fourier transform infrared spectrophotometry
HPLC	=	high-performance liquid chromatography
hr	=	hour (s)
i.e.	=	id est (that is)
IR	=	infrared
log	=	logarithm
M	=	molarity
mcm	=	micrometer (s)
mg	=	milligram (s)
min	=	minute (s)
ml	=	milliliter (s)
mPa·s	=	milliPascal second
MW	=	molecular weight
nm	=	nanometer (s)
No.	=	number of sample
o/w	=	oil in water emulsion
P407	=	poloxamer 407
pH	=	the negative logarithm of the hydrogen ion concentration

LIST OF ABBREVIATIONS (Cont.)

pKa	=	the negative logarithm of the dissociation constant
psi	=	pound (s) per square inch
R^2	=	coefficient of determination
R&D	=	research and development
RES	=	recticuloendothelial system
rpm	=	revolution (s) per minute
RT	=	retention time
SA	=	stearic acid
SD	=	standard deviation
SEM	=	scanning electron microscopy
SLN	=	solid lipid nanoparticles
T80	=	tween 80
TEM	=	Transmission electron microscopy
TM	=	tripalmitin
TP	=	tripalmitin
TS	=	tristearin
UV	=	ultraviolet
μg	=	microgram (s)
μl	=	microliter (s)
μm	=	micrometer (s)
λ_{max}	=	wavelength of maximum absorption
%	=	percentage
>	=	more than
<	=	less than
#	=	batch number