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FEASIBILITY STUDY ON PRONIOSOME DEVELOPMENT USING SAQUINAVIR MESYLATE AS A MODEL DRUG

Miss Rattana Srichaisak

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งานวิจัยนี้มีวัตถุประสงค์เพื่อศึกษาความเป็นไปได้ในการพัฒนาโพรนิโอโซมของซาควินาเวียมีไซเลท และคุณสมบัติทางเคมีกายภาพของโพรนิโอโซมและนิโอโซมที่เตรียมจากโพรนิโอโซม กลุ่มของสารลดแรงตึงผิวโพลีออกซีเอธิลีนอัลคิลอีเธอร์ถูกเลือกนำมาใช้เพื่อศึกษาความสามารถในการก่อนิโอโซมที่อุณหภูมิ 37 องศาเซลเซียสโดยใช้วิธีฟิลม์แห้งในการเตรียมนิโอโซม การเตรียมโพรนิโอโซมของซาควินาเวียมีไซเลททำโดยสองวิธีคือ การผสมสารกระจายตัวของนิโอโซมที่กักเก็บซาควินาเวียมีไซเลท หรือสารละลายของซาควินาเวียมีไซเลทร่วมกับสารลดแรงตึงผิวและไขมัน กับแล็กโทส หลังจากนั้นนำของผสมมาอบที่อุณหภูมิ 70 องศาเซลเซียสเป็นเวลา 24 ชั่วโมง และผ่านแร่งขนาด 30 เมช ทำการศึกษารูปร่าง การกระจายของขนาดอนุภาค คุณสมบัติการไหล และการปลดปล่อยยาออกจากแกรนูล จากการศึกษาพบว่าโพรนิโอโซมของซาควินาเวียมีไซเลทสามารถเตรียมจากทั้งสองวิธีข้างต้นโดยใช้อัตราส่วนโดยโมลระหว่างโพลีออกซิล 4 ลอริลอีเทอร์ คอเลสเตอรอล และโพลีเอธิลลีนไกลคอล 40 สเตียเรตเท่ากับ 70:0:30 ในความเข้มข้น 60 มิลลิโมลร่วมกับแล็กโทส ผลการทดลองพบว่าแกรนูลมีคุณสมบัติการไหลที่ไม่ดี แกรนูลสามารถเปลี่ยนรูปเป็นนิโอโซมได้เองในน้ำ กรดไฮโดรคลอริกเข้มข้น 0.1 นอร์มอล และฟอสเฟตบัฟเฟอร์พีเอช 6.8 ที่อุณหภูมิ 37 องศาเซลเซียส การปลดปล่อยยาจากโพรนิโอโซมเพิ่มขึ้นอย่างมีนัยสำคัญในกรดไฮโดรคลอริกเข้มข้น 0.1 นอร์มอล และฟอสเฟตบัฟเฟอร์พีเอช 6.8 ซาควินาเวียมีไซเลทในโพรนิโอโซมมีความคงตัวนาน 2 เดือนหลังเก็บที่อุณหภูมิ 45 องศาเซลเซียส ความชื้นสัมพัทธ์ 75±5% ดังนั้นจึงมีความเป็นไปได้ในการพัฒนาโพรนิโอโซมเพื่อเป็นระบบนำส่งยาทางปาก

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สาขาวิชา เภสัชอุตสาหกรรม	ลายมือชื่ออาจารย์ที่ปรึกษา จิตติมา ชัชวาลย์สายสินธ์
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RATTANA SRICHAISAK: FEASIBILITY STUDY ON PRONIOSOME DEVELOPMENT USING SAQUINAVIR MESYLATE AS A MODEL DRUG. THESIS ADVISOR: JITTIMA CHATCHAWALSAISIN, Ph.D., THESIS CO-ADVISOR: PONGSAKORNPAT ARUNOTHAYANUN, Ph. D., 177 pp. ISBN 974-17-4588-5.

In this study, the feasibility to develop proniosomes of saquinavir mesylate was investigated. The physicochemical properties of proniosomes and proniosome-derived niosomes were also studied. A series of polyoxyethylene alkyl ether surfactants were used to study the ability to form niosomes at 37°C in aqueous media by dry film method. Attempts were made to prepare saquinavir mesylate proniosomes by two methods: incorporating dispersion of drug entrapped niosomes or solution of drug and lipid/ surfactants into lactose, then oven-drying at 70°C for 24 h. The dried mass was screened through a 30 mesh sieve. The morphology, size distribution, flowability and drug release of granules were studied. The results showed that both methods could form saquinavir mesylate proniosomes with 60 mM of 70:0:30 mole ratio of polyoxyl 4 lauryl ether: cholesterol: polyethylene glycol 40 stearate and lactose. The granules possessed poor flowability. They could spontaneously transform to niosomes in water, 0.1N hydrochloric acid and phosphate buffer pH 6.8 at 37°C. The drug release from proniosomes in 0.1N hydrochloric acid and phosphate buffer pH 6.8 was significantly increased ($p<0.05$). Saquinavir mesylate loading proniosomes stored at 45°C and 75±5% relative humidity was stable up to 2 months. In conclusion, proniosomes could be produced and the system could be a candidate for oral drug delivery.

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LIST OF ABBREVATIONS

%	percentage
°C	degree Celsius (centrigrade)
µg	microgram (s)
µm	micrometer (s)
λ_{max}	wavelength of maximum absorption
AUC	area under the curve
CHOL	cholesterol
cm^{-1}	the reciprocal of centimeters (wave number)
CPP	critical packing parameter
CV	coefficient of variation
DSC	differential scanning calorimetry
e.g.	for example, exempli gratia
EE	entrapment efficiency
et.al.	et alli, and others
g	gram (s)
HLB	hydrophilic lipophilic balance
HPLC	high-performance liquid chromatography
h	hour (s)
HIV	human immunodeficiency virus
HSM	hot stage microscopy
i.e.	id est (that is)
IR	infrared
log	logarithm
log P	n-octanol/ water partition coefficient
mg	milligram (s)
min	minute (s)
ml	milliliter (s)
mM	millimolar (s)
MW	molecular weight
N	normality
NA	not applicable

PBS	phosphate buffer saline
pH	the negative logarithm of the hydrogen ion concentration
pKa	ionization constant
PXRD	powder X-ray diffractometry
r^2	coefficient of determination
rpm	revolution (s) per minute
R-SQV	recrystallized saquinavir mesylate
RT	retention time
SD	standard deviation
SEM	scanning electron microscopy
SF	surfactant
SM52	simulsol®M52
SQV	saquinavir mesylate
TEM	transmission electron microscopy
v/v	volume by volume
w/v	weight by volume
w/w	weight by weight