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DEVELOPMENT AND EVALUATION OF DILTIAZEM
HYDROCHLORIDE TRANSDERMAL DELIVERY SYSTEMS

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การพัฒนา ระบบนำส่งยาทางผิวหนังชนิดควบคุมการแพร่ด้วยเมทริกซ์ของดิลไทอะเซมไฮโดรคลอไรด์ เพื่อยืดการปลดปล่อย จากการศึกษาผลของ อัตราส่วนระหว่างไฮดรอกซีโพรพิลเมธิลเซลลูโลสกับ เอธิลเซลลูโลส ต่อ ความหนาและคุณสมบัติเชิงกลของฟิล์ม พบว่าทั้งอัตราส่วนระหว่าง พอลิเมอร์และชนิดของพลาสติกไซเซออร์ ไม่ส่งผลต่อความหนาของฟิล์ม แต่กลับส่งผลต่อคุณสมบัติเชิงกลของฟิล์ม ฟิล์มที่มีอัตราส่วนระหว่างพอลิเมอร์และชนิดของพลาสติกไซเซออร์ต่างกัน จะมีปริมาณยาต่างกัน ผลการประเมินความเข้ากันได้โดยเทียบความใสและภาพบริเวณผิวของฟิล์ม พบว่า ฟิล์มที่มีอัตราส่วนของเอธิลเซลลูโลสร้อยละ 60 ของน้ำหนักพอลิเมอร์ทั้งหมดจะเกิดการแยกของฟิล์ม ความเข้ากันได้ของฟิล์มยังขึ้นอยู่กับชนิดของสารเพิ่มการซึมผ่าน และยังพบว่า อัตราส่วนระหว่างพอลิเมอร์และชนิดของสารเพิ่มการซึมผ่าน มีผลต่อการดูดความชื้นของฟิล์ม ผลที่ได้จากขั้นการพัฒนาสูตรตำรับสัมพันธ์กับผลศึกษาการปลดปล่อยยาแบบภายนอกกาย จะนำไป ใช้ในการคัดเลือกสูตรตำรับที่จะทดสอบในขั้นตอนศึกษาการซึมผ่านผิวหนังแบบภายนอกกาย นำผลทดสอบที่ได้ไปคำนวณหาพารามิเตอร์ของการซึมผ่านผิวหนัง สุดท้าย จึงได้ระบบนำส่งยาทางผิวหนังที่เหมาะสมสำหรับดิลไทอะเซมไฮโดรคลอไรด์ ซึ่งเตรียมจาก ไฮดรอกซีโพรพิลเมธิลเซลลูโลสกับเอธิลเซลลูโลส อัตราส่วน 8 ต่อ 2 ใช้ ไดบิวทิลพทาเลตเป็นพลาสติกไซเซออร์ และมี ไอโซโพรพิลไมริสเตต ไอโซโพรพิลพาล์มมิเตต และ ทวิน 80 เป็นสารเพิ่มการซึมผ่าน

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The polymer matrix diffusion-controlled transdermal drug delivery systems were developed for sustained-release of diltiazem hydrochloride. The effect of various ratios of hydroxypropyl methylcellulose : ethylcellulose and types of plasticizer on the thickness and the mechanical properties were studied. It was found that the film thickness was not affected by both the polymeric ratios and plasticizer types, in the contrast with the mechanical properties. The drug contents with various polymeric ratios and the enhancer types were difference. The compatibilities of the ingredients in the film formulation were evaluated based on the transparency and the surface topography. The increasing of ethylcellulose ratio to 60% of total polymer weight resulted in separation of the film surface. Variety of enhancers affected the compatibility of the ingredients in the film formulations. Moisture uptake had also been tested. It was found that both the polymeric ratio and enhancer types affected the percentage of moisture uptake. The *in vitro* drug release and *in vitro* skin permeation of diltiazem hydrochloride were conducted. The relationship between formulation development and *in vitro* drug release study brought to the chosen formulations. The results from *in vitro* permeation study had been used in selection of the appropriate film formulations of diltiazem hydrochloride. The skin permeation parameter composed from the result calculation. Finally, the suitable transdermal drug delivery systems have been developed. The final film formulation including hydroxypropyl methylcellulose : ethylcellulose at the ratio of 8:2, dibutyl phthalate, and enhancers such as isopropyl myristate, isopropyl palmitate, and Tween 80.

Field of study.....Pharmaceutics..... Student's signature.....*Ekapol Limpongsa*
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LIST OF ABBREVIATIONS

°C	degree celsius (centigrade)
cm	centimeter (s)
cm ²	square centimeter (s)
cP	centipoises (s)
D	diffusion coefficient or diffusivity
DBP	dibutyl phthalate
DEP	diethyl phthalate
DTZ	diltiazem
e.g.	exempli gratia, for example
EC	ethylcellulose
et al.	et alii, and others
g	gram (s)
GI	gastrointestinal
HCl	hydrochloric acid or hydrochloride salt
HPLC	high performance liquid chromatography
HPMC	hydroxypropyl methylcellulose
hr	hour (s)
i.e.	id est, that is
IPM	isopropyl myristate
IPP	isopropyl palmitate
IR	infrared
IV	intravenous
J _{ss}	steady state flux
K	partition coefficient
L	liter (s)
m ²	square meter (s)

min	minute (s)
mg	milligram (s)
ml	milliliter (s)
m _p	melting point
mPa.s	millipascal per second (s)
MW	molecular weight
N	normality or normal
nm	nanometer (s)
NMP	N-methyl-2-pyrrolidone
OA	oleic acid
P _{app}	apparent permeation coefficient
PEG	polyethylene glycol 400
PG	propylene glycol
pH	the negative logarithm of the hydrogen ion concentration
pK _a	the negative logarithm of the dissociation constant
qs.	make to volume
r ²	coefficient of correlation
%RH	percentage of relative humidity
s	second (s)
SD	standard deviation
SEM	scanning electron microscopy
sp. gr.	specific gravity
TDS	transdermal delivery system
TEC	triethyl citrate
T _{lag}	lag time
Tw	Tween 80
USP	The United States Pharmacopoeia

UTS	ultimate tensile strength
UV	ultraviolet
v/v	volume by volume
w/v	weight by volume
w/w	weight by weight
μg	microgram (s)
μm	micrometer (s), micron (s)