

การพัฒนาสูตรคำรับยาเม็ดสารสกัดกวางเครื่องดัง

นายเพชรพงศ์ เพชรี

วิทยานิพนธ์นี้เป็นส่วนหนึ่งของการศึกษาตามหลักสูตรปริญญาโทสาขาวิชาสหเวชศาสตรมหาบัณฑิต

สาขาวิชาเภสัชอุตสาหกรรม ภาควิชาเภสัชอุตสาหกรรม

คณะเภสัชศาสตร์ จุฬาลงกรณ์มหาวิทยาลัย

ปีการศึกษา 2549

ลิขสิทธิ์ของจุฬาลงกรณ์มหาวิทยาลัย

FORMULATION DEVELOPMENT OF *BUTEA SUPERBA* EXTRACT TABLETS

Mr.Petchpong Petcharee

**A Thesis Submitted in Partial Fullfillment of the Requirements
for the Degree of Master of Science in Pharmacy Program in Industrial Pharmacy**
Department of Manufacturing Pharmacy
Faculty of Pharmaceutical Sciences
Chulalongkorn University
Academic Year 2006
Copyright of Chulalongkorn University

492127

Thesis Title **FORMULATION DEVELOPMENT OF BUTEA
SUPERBA EXTRACT TABLETS**

By **Mr.Petchpong Petcharee**

Field of Study **Industrial Pharmacy**

Thesis Advisor **Professor Garnpimol C.Rithidej, Ph.D.**

Thesis Co-advisor **Associate Professor Chaiyo Chaichantipyuth, Ph.D.**

Accepted by the Faculty of Pharmaceutical Sciences, Chulalongkorn University in Partial Fulfillment of the Requirements for the Master's Degree

Pornpen Pramyo Dean of the Faculty of Pharmaceutical Sciences
(Associate Professor Pornpen Pramyothin, Ph.D.)

THESIS COMMITTEE

Wichein Thanindrata Chairman

(Assistant Professor Wichein Thanindrata, M.Sc. in Pharm.)

Garnpimol C. Rithidej Thesis Advisor

(Professor Garnpimol C. Ritthidej, Ph.D.)

Chaiyo Chaichantipyuth Thesis Co-advisor

(Associate Professor Chaiyo Chaichantipyuth, Ph.D.)

Rapepol Bavovada Member

(Associate Professor Rapepol Bavovada, Ph.D.)

Narueporn Sutanthavibul Member

(Narueporn Sutanthavibul, Ph.D.)

เพชรพงศ์ เพชรี : การพัฒนาสูตรตำรับยาเม็ดสารสกัดกวัวเครื่อง。
(FORMULATION DEVELOPMENT OF BUTEA SUPERBA EXTRACT TABLETS) อ. ที่ปรึกษา: ศาสตราจารย์ ดร.กาญจน์พิมล ฤทธิเดช, อ. ที่ปรึกษา
 ร่วม: รองศาสตราจารย์ ดร.ชัยโย ชัยชาญพิพุทธ, 112 หน้า.

การพัฒนาสูตรตำรับยาเม็ดสารสกัดกวัวเครื่อง โดยมี Medicarpin (เมดิคาร์ปิน) มาใช้เป็นสารบ่งคุณภาพในการควบคุมคุณภาพในการพัฒนาสูตรตำรับยาเม็ดสารสกัดกวัวเครื่อง โดยยาเม็ดสารสกัด 2 สูตรตำรับ ประกอบด้วย 1) สารสกัด กวัวเครื่องใน 50% เอทานอล, แป้งมันสำปะหลัง, แป้งข้าวโพด, อาไวเซล พีเอช 102, แอคไಡซอล, แอโรซิล, และ สเตเรียริก เอเซิล 2) สารสกัดกวัวเครื่องใน 95% เอทานอล, แป้งมันสำปะหลัง, แอคไಡซอล, แอโรซิล, และ สเตเรียริก เอเซิล ซึ่งทั้ง 2 สูตร ตำรับให้แกรนูลที่มีการยึดเกาะและการไหลที่ดี มีกลิ่นหอม และสามารถนำไปตอกอัด เป็นเม็ดได้ เมื่อประเมินคุณภาพของสูตรยาเม็ดที่ได้รับการคัดเลือกทางเคมีฟิสิกส์ พบว่า ความแข็ง, ความกร่อน, ความแปรปรวนของน้ำหนักเม็ดยา, การแตกตัวของเม็ดยา, ความสม่ำเสมอของปริมาณสารสำคัญ และการละลายตัวของเม็ดยา มีคุณสมบัติเข้าตามเกณฑ์ ของเกสซ์ตำรับของเมริกา ฉบับที่ 29 นอกจากนี้ในสูตรตำรับ ยาเม็ดสารสกัดกวัวเครื่อง ใน 50% เอทานอล ที่ผ่านการเก็บในโถแก้วรักษาความชื้นเป็นเวลา 1 ปี 10 เดือน พบว่ามีการเปลี่ยนแปลงน้อยมาก โดยเฉพาะปริมาณของปริมาณเมดิคาร์ปิน

ภาควิชา	เภสัชอุตสาหกรรม	ลายมือชื่อนิสิต	นางสาวนงนัช นนท์
สาขาวิชา	เภสัชอุตสาหกรรม	ลายมือชื่ออาจารย์ที่ปรึกษา	ดร. ชัยโย ชัยชาญพิพุทธ
ปีการศึกษา	2549	ลายมือชื่ออาจารย์ที่ปรึกษาร่วม	ดร.ชัยโย ชัยชาญพิพุทธ

MAJOR INDUSTRIAL PHARMACY

KEY WORDS: *BUTEA SUPERBA* ROXB. / *BUTEA SUPERBA* EXTRACT TABLETS / FLAVONOID / MEDICARPIN

PETCHPONG PETCHAREE: FORMULATION DEVELOPMENT OF *BUTEA SUPERBA* EXTRACT TABLETS. THESIS ADVISOR: PROFESSOR GARNPIMOL C. RITTHIDEJ, Ph.D., THESIS COADVISOR: ASSOCIATE PROFESSOR CHAIYO CHAICHANTIPYUTH, Ph.D., 112 pp.

Medicarpin were used as active marker to quality control in formulation development of *Butea superba* extract tablets. The investigated 2 formulations of *Butea superba* extract tables were 1) *Butea superba* extract in 50% ethanol, tapioca starch, corn starch, Avicel[®] PH102, Ac-di-sol[®], stearic acid and Aerosil[®]. 2) *Butea superba* extract in 95% ethanol, tapioca starch, Ac-di-sol[®], stearic acid and Aerosil[®]. Both formulations showed a good agglomerated granules, flowablility, odour, and had excellent compressibility for tableting. The physicochemical properties of selected formulation of *Butea superba* extract tablets such as hardness, friability, weight variation, disintegration, dissolution, content uniformity and active ingredient content were conformed to the specification of USP29. In addition the stability study of 50% ethanol *Butea superba* extract tablets stored in desiccator under ambient condition for 1 year and 10 months showed that the property of tablets were unchanged especially the content of medicarpin.

Department	Manufacturing Pharmacy	Student's signature	Petchpong Petcharee
Field of study	Industrial Pharmacy	Advisor's signature	Garnpimol C. Ritthidej
Academic year	2006	Co-advisor's signature	Chaiyo Chaichantipyuth

ACKNOWLEDGEMENTS

I would like to express my sincere gratitude to my thesis advisor, Professor Garipimol C. Ritthidej, Ph.D. for her excellent meaningful advices, invaluable guidance and encouragement throughout my investigation. Her patience, kindness and understanding are also deeply appreciated.

I am also indebted to Associate Professor Chaiyo Chaichantipyuth, Ph.D., for his meaningful comment, treatment, invaluable guidance and encouragement throughout my thesis.

I wish to express appreciation to Associate Professor Rapepol Bavovada, Ph.D. for his grateful advises, invaluable guidance and interest in my investigation.

I would like to acknowledge the thesis committee as Assistant Professor Wichein Thanindrataarn, M.Sc. in Pharm., Associate Professor Rapepol Bavovada, Ph.D. and Narueporn Sutanthavibul, Ph.D. for their valuable suggestion and comment.

I am also thankful to all teachers and staffs at the Faculty of Pharmaceutical Sciences, Chulalongkorn University, especially the staff of Department of the Manufacturing Pharmacy, Pharmaceutical Botany, Pharmacognosy, Pharmacology, Pharmaceutical Chemistry and Central laboratory for their assistant and support.

I wish to express my thanks to all my friends in and out the laboratory whose names have not been mentioned for their help and encouragement during experiment.

I wish to express appreciation for finance support of the research grant from Graduate school of Chulalongkorn University.

Finally, I would like to thank my father, my mother, my grandmother, my sister and my cousin for their endless love, kindness, understanding, continuous support, careful, encouragement and cheerfulness throughout my graduate study.

CONTENTS

	Page
ABSTRACT (THAI).....	iv
ABSTRACT (ENGLISH).....	v
ACKNOWLEDGEMENT.....	vi
CONTENTS.....	vii
LIST OF TABLES.....	viii
LIST OF FIGURES.....	x
LIST OF SCHEMES.....	xiii
LIST OF ABBRIVIATIONS.....	xiv
CHAPTER	
I INTRODUCTION.....	1
II LITERATURE REVIEW.....	3
III EXPERIMENTAL.....	26
IV RESULTS AND DISCUSSION.....	41
V CONCLUSIONS.....	88
REFERENCES.....	90
APPENDICES.....	98
VITA.....	112

LIST OF TABLES

Table	Page
1. Commercialization of herbs and drugs: Regulatory differences.....	6
2. Characterization of <i>Butea superba</i> Roxb. compared with <i>Pueraria mirifica</i> Airy Shaw et Suvatabandhu.....	8
3. Steps in different methods of tablets manufacture	18
4. Tablet filler.....	20
5. Binders commonly used in wet granulation	21
6. Lubricants used in solid dosage form.....	22
7. Disintegrant used in solid dosage form.....	23
8. Commonly used glidants and usual concentration range.....	23
9. Combined fractions from the dichloromethane extract.....	32
10. Combined fractions from fraction C2.....	32
11. Combined subfractions from fraction C2.1.....	33
12. Formulation composition of <i>Butea superba</i> 95% ethanol dry extract.....	35
13. Formulation composition of <i>Butea superba</i> 50% ethanol dry extract.....	35
14. Formulation composition of <i>Butea superba</i> 95% and 50% ethanol extract tablets.....	39
15. ^{13}C -NMR and ^1H -NMR data of BS1 and previously reported.....	48
16. Calibration data of medicarpin in methanol solution at 287 nm.....	103
17. Water content in <i>Butea superba</i> fluid extract.....	104
18. The organoleptic property of dry powder <i>Butea superba</i> extract.....	59
19. The moisture content of dry powder <i>Butea superba</i> extract.....	105
20. Bulk density, Tapped density and Carr's index of dry powder of <i>Butea superba</i> 50% and 95% ethanolic extracts.....	105
21. Description flowability by Carr's index.....	62
22. Flow rates of dry extract of <i>Butea superba</i> 50% and 95% ethanolic granules.....	106
23. Content uniformity of 50% ethanolic <i>Butea superba</i> fluid extracts.....	65
24. Content uniformity of 50% ethanolic <i>Butea superba</i> extracts granules (F5-BS-50).....	96

Table	Page
25. Content uniformity of 95% ethanolic <i>Butea superba</i> fluid extracts.....	67
26. Content uniformity of 95% ethanolic <i>Butea superba</i> extract granules (F1-BS-95).....	68
27. Diameter and thickness of <i>Butea superba</i> 50% and 95% ethanolic extract tablet compared to Dokwhan® tablets (DW).....	107
28. Formulation of <i>Butea superba</i> extract tablets.....	72
29. Friability of <i>Butea superba</i> 50% and 95% ethanolic extract tablet compared to Dokwhan® tablets (DW).....	108
30. Hardness of <i>Butea superba</i> 50% and 95% ethanolic extract tablets compared to Dokwhan® tablets (DW).....	109
31. Weight variation of <i>Butea superba</i> 50% and 95% ethanolic extract tablets compared to Dokwhan® tablets (DW).....	110
32. Disintegration time of <i>Butea superba</i> 50% and 95% ethanolic extract tablets compared to Dokwhan® tablets (DW).....	111
33. Overall physical examination of formulation of <i>Butea superba</i> extract tablets and Dok-wan® tablets (DW).....	76
34. Content uniformity of 50% ethanolic <i>Butea superba</i> extract tablets.....	79
35. Content uniformity of 95% ethanolic <i>Butea superba</i> extract tablets.....	80
36. Dissolution of 50% and 95% ethanolic <i>Butea superba</i> extract tablets (F5-BS-50 and F1-BS-95).....	111
37. Content uniformity of 50% ethanolic <i>Butea superba</i> extract tablets 1 year and 10 months.....	85

LIST OF FIGURES

Figure	Page
1. Various parts of <i>Butea superba</i> Roxb.....	7
2. The Remedy Pamphlet of Kwao krua tuber of Loung – Anusamsoontorn.....	9
3. Chemical structure of pterocarpans.....	14
4. Chemical structure of medicarpin.....	15
5. Wet granulation processes.....	19
6. Coarse powder of <i>Butea superba</i> Roxb.....	41
7. Dark-red gummy of <i>Butea superba</i> 95%ethanolic extract.....	41
8. Figure prints of <i>Butea superba</i> 95%ethanolic extract by TLC.....	42
9. TLC figure prints of compound BS 1.....	43
10. BS 1 which was whitish powder.....	43
11. Mass spectrum of BS 1.....	44
12. ¹³ C-NMR spectrum of BS 1.....	45
13. ¹ H-NMR spectrum of BS 1.....	46
14. DEPT spectrum of BS 1.....	99
15. HMQC spectrum of BS 1.....	100
16. HMBC spectrum of BS 1.....	101
17. COSY spectrum of BS 1.....	102
18. Numbering of chemical structure of medicarpin.....	47
19. Maximum wave length of BS 1.....	49
20. HPLC chromatogram of BS 1.....	50
21. Linearity curves of the peak area versus the concentrations of medicarpin.....	51
22. <i>Butea superba</i> 50% ethanolic extracts.....	52
23. TLC patterns of <i>Butea superba</i> 50% ethanolic extracts.....	52
24. The water content of 50% and 95% ethanol <i>Butea superba</i> fluidextracts.....	53
25. Dry granules extract produced of the ratios of liquid extract and excipient of 1:1, 1:2 and 1:3.....	55
26. <i>Butea superba</i> extract with lactose and starch in the ratio 1:2.....	55
27. Granules of <i>Butea superba</i> extracts as 50% ethanolic extract and 95% ethanolic extract.....	56
28. Moisture content of dry powder <i>Butea superba</i> extract.....	57

Figure	Page
29. Bulk density of dry powder <i>Butea superba</i> extract.....	60
30. Tapped density of dry powder <i>Butea superba</i> extract.....	61
31. Carr's index of all dry powder <i>Butea superba</i> extract formulation.....	63
32. Flow rates of dry extract <i>Butea superba</i> granules.....	64
33. HPLC Chromatogram as 95% ethanolic fluidextracts and 50% ethanolic fluid extracts.....	69
34. Physical characteristics of <i>Butea superba</i> tablets as 50% ethanolic extract tablets, 95% ethanolic extract tablets and Dokwhan® tablets.....	71
35. Friability of <i>Butea superba</i> extract tablet compared to Dokwhan® tablets (DW).....	73
36. Hardness of <i>Butea superba</i> extract tablets compared to Dokwhan® tablets (DW).....	74
37. Weight variation of <i>Butea superba</i> extract tablets compared to Dokwhan® tablets (DW).....	74
38. Disintegration time of <i>Butea superba</i> extract tablets compared to Dokwhan® tablets (DW).....	75
39. HPLC chromatogram of Dokwhan® tablets.....	77
40. HPLC chromatogram of <i>Butea superba</i> 95% ethanolic extract tablet (F1-BS-95).....	78
41. HPLC chromatogram of <i>Butea superba</i> 50% ethanolic extract tablet (F5-BS-50).....	78
42. The comparisons of medicarpin were 50% and 95% ethanolic <i>Butea superba</i> extracts in 3 dosage form.....	81
43. Dissolution of 50% ethanolic <i>Butea superba</i> extract tablets.....	82
44. Dissolution of 95% ethanolic <i>Butea superba</i> extract tablets.....	82
45. Physical appearance of F5-50 <i>Butea superba</i> extract tablets as freshly prepared and 1 year and 10 months.....	84
46. Content uniformity of <i>Butea superba</i> extract tablets, freshly prepared and stored tablets.....	86

Figure	Page
47. Friability of <i>Butea superba</i> extract tablets, freshly prepared and stored tablets.....	86
48. Hardness of <i>Butea superba</i> extract tablets, freshly prepared and stored tablets.....	87
49. Disintegration time of <i>Butea superba</i> extract tablets, freshly prepared and stored tablets.....	87

LIST OF SCHEMES

Scheme	Page
1. Extraction of the dried tuber of <i>Butea superba</i> Roxb.....	31

LIST OF ABBREVIATIONS

BS	=	<i>Butea superba</i>
°C	=	Degree Celsius
CC	=	Column Chromatography
CDCl ₃	=	Deuterated Chloroform
CH ₂ Cl ₂	=	Dichloromethane
cm	=	Centimeter
¹³ C NMR	=	Carbon-13 Nuclear Magnetic Resonance
COSY	=	Correlated Spectroscopy
δ	=	Chemical Shift
<i>d</i>	=	Doublet (for NMR spectra)
<i>dd</i>	=	Doublet of Doublets (for NMR spectra)
<i>ddd</i>	=	Doublet of Doublets of Doublets (for NMR spectra)
DEPT	=	Distortionless Enhancement by Polarization Transfer
EIMS	=	Electron Impact Mass Spectrum
EtOAc	=	Ethyl acetate
<i>g</i>	=	Gram
μg	=	Microgram
hr.	=	Hour
<i>hept</i>	=	Heptet (for NMR spectra)
¹ H NMR	=	Proton Nuclear Magnetic Resonance
HMBC	=	¹ H-detected Heteronuclear Multiple Bond Coherence
Hz	=	Hertz
<i>J</i>	=	Coupling Constant
kg	=	Kilogram
L	=	Liter
<i>m</i>	=	Multiplet (for NMR spectra)
m	=	Meter
M ⁺	=	Molecular Ion
MeOH	=	Methanol
mg	=	Milligram

MHz	=	Megahertz
min	=	Minute
ml	=	Milliliter
mm	=	Millimeter
<i>m/z</i>	=	Mass to charge ratio
MS	=	Mass Spectrometry
nm	=	Nanometer
NMR	=	Nuclear Magnetic Resonance
<i>s</i>	=	Singlet (for NMR spectra)
<i>t</i>	=	Triplet (for NMR spectra)
TLC	=	Thin Layer Chromatography
%w/w	=	Percentage weight by weight