PREPARATION AND EVALUATION OF DRUG RELEASE CHARACTERISTIC OF CROSSLINKED CHITOSAN/SILK FIBROIN BLEND FILMS



Mr. Sopon Kruaykitanon

A Thesis Submitted in Partial Fulfilment of the Requirements
for the Degree of Master of Science

The Petroleum and Petrochemical College, Chulalongkorn University
in Academic Partnership with

The University of Michigan, The University of Oklahoma,
and Case Western Reserve University

2002

ISBN 974-03-1616-6

Thesis Title: Preparation and Evaluation of Drug Release

Characteristic of Crosslinked Chitosan/Silk Fibroin

Blend Films

By : Mr. Sopon Kruaykitanon

Program : Polymer Science

Thesis Advisors : Dr. Ratana Rujiravanit

Prof. Alexander M. Jameison

Accepted by the Petroleum and Petrochemical College, Chulalongkorn University, in partial fulfilment of the requirements for the Degree of Master of Science.

K. Brunyahint. College Director

(Assoc. Prof. Kanchana Bunyakiat)

Thesis Committee:

(Dr. Ratana Rujiravanit)

Rahma Rummmit

(Prof. Alexander M. Jameison)

(Asst. Prof. Suwabun Chirachanchai)

must Servial

(Assoc. Prof. Anuvat Sirivat)

ABSTRACT

4372019063 : POLYMER SCIENCE PROGRAM

Sopon Kruaykitanon: Preparation and Evaluation of Drug Release Characteristic from Crosslinked Chitosan/Silk Fibroin Blend Films. Thesis Advisors: Dr. Ratana Rujiravanit and Prof. Alexander M.

Jameison, 114 pp. ISBN 974-03-1616-6

Keywords : Chitosan/ Silk Fibroin/ Blend Film/ Drug Release

Crosslinked chitosan/silk fibroin blend films were prepared by solution casting using glutaraldehyde as crosslinking agent. Drug release characteristics of the blend films with various blend compositions were investigated. Theophylline, diclofenac sodium, amoxicillin trihydrate and salicylic acid were used as model drugs. The release studies were carried out at 37°C in buffer solutions at pH 2.0, 5.5 and 7.2. It was found that the blend film with 80% chitosan content showed the maximum amount of drug release at pH 2.0 for all types of drugs. From swelling study, the maximum degree of swelling of the drug-loaded blend films was also obtained at pH 2.0 and 80 % chitosan content. The amounts of drugs released from films with 80% chitosan content were in the order: salicylic acid > theophylline> diclofenac sodium > amoxicillin. The maximum amount of salicylic acid, theophylline, diclofenac sodium and amoxicillin release from blend films with 80% chitosan content at pH 2.0 were 92.7%, 81.1%, 76.6%, and 37.2%, respectively.

บทคัดย่อ

โสภณ กรวยกิตานนท์ : การเตรียมและการศึกษาการปลดปล่อยของยาของฟิล์มพอลิ เมอร์ผสมที่มีโครงสร้างเป็นร่างแห (Preparation and Evaluation of Drug Release Characteristic of Crosslinked Chitosan/Silk Fibroin Blend Films) อ.ที่ปรึกษา : คร.รัตนา รุจิรวนิช และ ศ. อเลก ซานเคอร์ เอม เจมิสัน 114 หน้า ISBN 974-03-1616-6

งานวิจัยนี้เป็นการเตรียมฟิล์มพอลิเมอร์ผสมที่มีโครงสร้างเป็นแบบร่างแหใช้เทคนิคdkig การเตรียมด้วยสารละลาย ระหว่างใคโตซานและซิลค์ไฟโบรอิน โดยใช้กลูตารัลดีไฮด์เป็นสารที่ เพื่อศึกษาลักษณะการปลดปล่อยของยาจากพอลิเมอร์ผสมที่อัตราส่วน ก่อให้เกิดการเชื่อมโยง ต่างๆกัน ในงานวิจัยนี้ได้เลือกใช้ ที่โอไฟลิน กรดซาลิไซลิก ไดโคลฟีแนคโซดียม และอมอกซีซิ ลิน เป็นยาต้นแบบ คคยศึกาาการปลดปล่อยของยา ณ อุณหภูมิ 37 องศาเซลเซียส ในสารละลายที่มี ค่าความเป็นกรคค่างคงที่ที่พีเอช 2.0 5.5 และ 7.2 ตามลำคับ จากงานวิจัยนี้พบว่า สำหรับยาต้น แบบทุกชนิด ปริมาณยาที่ปลดปล่อยออกจากฟิล์มพอลิเมอร์ผสมมีปริมาณสูงสุด เมื่อฟิล์มผสมมี ปริมาณไคโตซานเป็นองค์ประกอบในฟิล์มอยู่ร้อยละ 80 ในสารละลายที่มีค่าพีเอช เป็น 2.0 เมื่อ ้ศึกษาระดับการบวมตัวของฟิล์มพอลิเมอร์ผสมที่มียาค้นแบบผสมอยู่ พบว่าระดับการบวมตัวของ ฟิล์มพอลิเมอร์ผสมเป็นไปในทำนองเคียวกัน นั่นคือมีอัตราการบวมตัวสูงสุดเมื่อฟิล์มผสมมี ปริมาณใคโตซานเป็นองค์ประกอบในฟิล์มอยู่ร้อยละ 80 ในสารละลายที่มีค่าพีเอชเป็น 2.0 เมื่อ เปรียบเทียบปริมาณยาแต่ละชนิดที่ปลดปล่อยออกมาจากฟิล์มพอลิเมอร์ผสมที่มีปริมาณไคโตซาน เป็นองค์ประกอบร้อยละ 80 พบว่า ปริมาณของซาลิไซลิกที่ปลดปล่อยออกจากฟิล์มผสมมีมากกว่า ที่โอไฟลีน ใดโคลฟีแนคโซเคียมและอมอกซีซิลิน ตามลำคับ ปริมาณสูงสุดของกรคซาลิไซลิก ที่ โอไฟลิน ใคโคลฟีแนคโซเคียม และอมอกซิซิลินที่ถูกปลดปล่อยออกจากฟิล์มผสมที่มีปริมาณใค โตซานอยู่ร้อยละ 80 ณ พีเอช 2 คิดเป็นอัตราร้อยละ 92.7 81.1 76.6 และ 37.2 ตามลำคับ

ACKNOWLEDGEMENTS

I would like to thank the Petroleum and Petrochemical College, Chulalongkorn University, where I have gained my knowledge and enriched my skill in polymer science. I would also like to acknowledge Surapon Food Public Company for their support of shrimp shells, the raw material used throughout this work. Also, I would like to thank KPT Cooperation (Thailand) for their supplying 50%w/w of NaOH solution, the chemical reagent that utilized for preparation of chitosan.

I would like to express grateful appreciation to my advisors, Dr. Ratana Rujiravanit, Prof. Alexander M. Jameison, and Prof. Seichi Tokura for their invaluable suggestion and criticism.

I am also indebted to my family and friends for their encouragement and understanding during my studies and thesis work.

TABLE OF CONTENTS

		PAGE
	Title Page	i
1	Abstract (in English)	iii
1	Abstract (in Thai)	iv
1	Acknowledgements	v
-	Table of Contents	vi
]	List of Tables	ix
1	List of Figures	xiv
CHAPT	TER	
I	INTRODUCTION	1
	1.1 Theoretical Background	2
	1.1.1 Controlled Drug Delivery	2
	1.1.1.1 Diffusion controlled release	2
	1.1.1.2 Swelling controlled release	5
	1.1.1.3 Erosion controlled release	7
	1.1.2 Chitin and Chitosan	7
	1.1.3 Silk Fibroin	10
II	LITERATURE SURVEY	12
	2.1 Chitosan-Based Polymer Blend	12
	2.2 Silk Fibroin- Based Blend Films	13
	2.3 Chitosan/Silk Fibroin Blend Films	14
	2.4 Chitosan-Based Materials for Drug	
	Delivery Studies	15
	2.5 Silk Fibroin-Based Materials for Drug	
	Delivery Studies	16
II	I EXPERIMENTAL	18
	3.1 Materials	18
	3.2 Equipment	18

CHAPTER		PAGE
	3.2.1 Retsch Sieving Machine	18
	3.2.2 Capillary Viscometer	18
	3.2.3 FTIR Spectrophotometer	19
	3.2.4 UV/VIS Spectrophotometer	19
	3.3 Methodology	19
	3.3.1 Preparation of Chitin	19
	3.3.2. Preparation of Chitosan	19
	3.3.3 Degree of Deacetylation of Chitosan	20
	3.3.4 Viscosity Average Molecular Weight	
	of Chitosan	20
	3.3.5 Preparation of Chitosan Solution	21
	3.3.6 Preparation of Drug-Loaded Blend Films	21
	3.3.7 Drug Release Studies	21
IV	RESULTS AND DISCUSSION	23
	4.1 Effect of Blend Composition on Drug Release	23
	4.2 Effect of pH on Drug Release	27
	4.3 Effect of Drug Types on Drug Release	28
	4.4 Effect of Immersion Time on Drug Release	30
	4.5 Effect of Concentration of Crosslinking Agent on	
	Drug Release	34
V	CONCLUSIONS	37
	REFERENCES	38
	APPENDICES	42
	Appendix A Preparation of chitosan	42
	Appendix B Characterization of chitosan	44
	Appendix C Determination of molecular weight of chitosan	45

CHAPTER		PAGE
	Appendix D UV spectrum of model drugs and glutaraldehyde	47
	Appendix E Calibration curve of model drugs	50
	Appendix F Data of drug release	54
	CURRICULUM VITAE	114

LIST OF TABLES

TABL	E	PAGE
1.1	Environmentally sensitive polymers for drug delivery	6
4.1	Degree of swelling and percent weight loss of	
	drug- loaded crosslinked chitosan and blend films	26
4.2	Initial rate of drug release from the blend films	
	with 80% chtiosan content	33
4.3	Degree of swelling and percent weight loss of	
	salicylic acid- loaded blend films with 80% chitosan	
	containing various glutaraldehyde concentrations	35
A1	Yields of chitin produced from shrimp shell	43
A2	Conversion of chitosan from chitin	44
B1	FTIR characteristics absorption bands of chitosan	45
C1	Running time of solvent and chitosan solution	45
C2	Data of relative viscosity (η_{rel}), specific viscosity (η_{sp}),	
	reduced viscosity (η _{red}).	46
D1	Summary of maximum wavelength (λ_{max}) of each type	
	of model drug and glutaraldehyde	49
E1	Data of calibration curve of theophylline solution.	50
E2	Data of calibration curve of diclofenac sodium solution	51
E3	Data of calibration curve of amoxicillin trihydrate solution.	52
E4	Data of calibration curve of salicylic acid solution	53
F1	Release of theophylline from crosslinked chitosan film at pH 2.0	54
F2	Release of theophylline from The blend films with 80%	
	chitosan content at pH 2.0	55
F3	Release of theophylline from the blend films with 60%	
	chitosan content at pH 2.0	56

[ABL]	E	PAGE
F4	Release of theophylline from the blend films with 50%	
	chitosan content at pH 2.0	57
F5	Release of theophylline from the blend films with 40%	
	chitosan content at pH 2.0	58
F6	Release of theophylline from chitosan films at pH 5.5	59
F7	Release of theophylline from the blend films with 80%	
	chitosan content at pH 5.5	60
F8	Release of theophylline from the blend films with 60%	
	chitosan content at pH 5.5	61
F9	Release of theophylline from the blend films with 50%	
	chitosan content at pH 5.5	62
F10	Release of theophylline from the blend films with 40%	
	chitosan content at pH 5.5	63
F11	Release of theophylline from chitosan films at pH 7.2.	64
F12	Release of theophylline from blend films with 80%	
	chitosan content at pH 7.2	65
F13	Release of theophylline from blend films with 60%	
	chitosan content at pH 7.2	66
F14	Release of theophylline from blend films with 50%	
	chitosan content at pH 7.2	67
F15	Release of theophylline from blend films with 40%	
	chitosan content at pH 7.2	68
F16	Release of amoxicillin from chitosan films at pH 2.0	69
F17	Release of amoxicillin from the blend films with 80%	
	chitosan content at pH 2.0	70
F18	Release of amoxicillin from the blend films with 60%	
	chitosan content at pH 2.0	71
F19	Release of amoxicillin from the blend films with 50%	
	chitosan content at pH 2.0	72

TABLE		PAGE
F20	Release of amoxicillin from the blend films with 40%	
F20	chitosan content at pH 2.0	73
F21	Release of amoxicillin from chitosan films at pH 5.5	73 74
F21		74
ΓΖΖ		75
F23	chitosan content at pH 5.5 Release of amoxicillin from the blend films with 60%	73
Γ23		76
F24	chitosan content at pH 5.5 Release of amoxicillin from the blend films with 50%	70
Г24		77
E26	chitosan content at pH 5.5	//
F25	Release of amoxicillin from the blend films with 40%	70
F2.6	chitosan content at pH 5.5	78 70
F26	1	79
F27	Release of amoxicillin from the blend films with 80%	90
F20	chitosan content at pH 7.2	80
F28		0.1
	chitosan content at pH 7.2	81
F29		
	chitosan content at pH 7.2	82
F30	Release of amoxicillin from the blend films with 40%	
	chitosan content at pH 7.2	83
F31	Release of salicylic acid from chitosan films content	
	at pH 2.0	84
F32	Release of salicylic acid from the blend films with 80%	
	chitosan content at pH 2.0	85
F33	Release of salicylic acid from the blend films with 60%	
	chitosan content at pH 2.0	86
F34	Release of salicylic acid from the blend films with 50%	
	chitosan content at pH 2.0	87
F35	Release of salicylic acid from the blend films with 40%	
	chitosan content at pH 2.0	88

ΓABLI	${f E}$	PAGE
F36	Release of salicylic acid from chitosan films content at pH 5.5	89
F37	Release of salicylic acid from the blend films with 80%	
	chitosan content at pH 5.5	90
F38	Release of salicylic acid from the blend films with 60%	
	chitosan content at pH 5.5	91
F39	Release of salicylic acid from the blend films with 50%	
	chitosan content at pH 5.5	92
F40	Release of salicylic acid from the blend films with 40%	
	chitosan content at pH 5.5	93
F41	Release of salicylic acid from chitosan films content	
	at pH 7.2	94
F42	Release of salicylic acid from the blend films with 80%	
	chitosan content at pH 7.2	95
F43	Release of salicylic acid from the blend films with 60%	
	chitosan content at pH 7.2	96
F44	Release of salicylic acid from the blend films with 50%	
	chitosan content at pH 7.2	97
F45	Release of salicylic acid from the blend films with 40%	
	chitosan content at pH 7.2	98
F46	Release of diclofenac sodium from chitosan films at pH 2.0	99
F47	Release of diclofenac sodium from the blend films	
	with 80% chitosan content at pH 2.0	100
F48	Release of diclofenac sodium from the blend films	
	with 60% chitosan content at pH 2.0	101
F49	Release of diclofenac sodium from the blend films	
	with 50% chitosan content at pH 2.0	102
F50	Release of diclofenac sodium from the blend films	
	with 40% chitosan content at pH 2.0	103

ΓABLI	E	PAGE
F51	Release of diclofenac sodium from chitosan films at pH 5.5	104
F52	Release of diclofenac sodium from the blend films	
	with 80% chitosan content at pH 5.5	105
F53	Release of diclofenac sodium from the blend films	
	with 60% chitosan content at pH 5.5	106
F54	Release of diclofenac sodium from the blend films	
	with 50% chitosan content at pH 5.5	107
F55	Release of diclofenac sodium from the blend films	
	with 40% chitosan content at pH 5.5	108
F56	Release of diclofenac sodium from chitosan films at pH 7.2	109
F57	Release of diclofenac sodium from the blend films	
	with 80% chitosan content at pH 7.2	110
F58	Release of diclofenac sodium from the blend films	
	with 60% chitosan content at pH 7.2	111
F 5 9	Release of diclofenac sodium from the blend films	
	with 50% chitosan content at pH 7.2	112
F60	Release of diclofenac sodium from the blend films	
	with 40% chitosan content at pH 7.2	113

LIST OF FIGURES

FIGURE		PAGE
1.1	.1 Drug level in the blood from (a) traditional drug	
	administration and (b) controlled delivery dosing	3
1.2	Drug delivery from a typical matrix drug delivery system	4
1.3	Drug delivery from environmentally sensitive release systems	6
1.4	Drug delivery from (a) bulk erosion and	
	(b) surface erosion systems	7
1.5	Chemical structure of chitin	8
1.6	Chemical structure of chitosan	9
1.7	Model of microstructure of silk fibroin	10
4.1	Effect of blend composition at various pH on releasing of	
	diclofenac sodium	23
4.2	Effect of blend composition at various pH on releasing of	
	salicylic acid	24
4.3	Effect of blend composition at various pH on releasing of	
	amoxicillin	24
4.4	Effect of blend composition at various pH on releasing of	
	theophylline	25
4.5	Comparison of the amounts of drugs released from chitosan	
	and the blend film with 80% chitosan content at pH 2.0	28
4.6	Comparison of the amounts of drugs released from chitosan	
	and the blend film with 80% chitosan content at pH 5.5	29
4.7	Comparison of the amounts of drugs released from chitosan	
	and the blend film with 80% chitosan content at pH 7.2	30
4.8	Chemical structure of anhydrous theophylline	30
4.9	Chemical structure of salicylic acid	30
4.10	Chemical structure of diclofenac sodium	31
4 11	Chemical structure of anhydrous theophylline	31

FIGURE		PAGE
4.12	Drug release profiles from the blend films with 80% chitosan	
	content at pH 2.0	32
4.13	Drug release profiles from the blend films with 80% chitosan	
	content at pH 5.5	32
4.14	Drug release profiles from the blend films with 80% chitosan	
	content at pH 2.0	33
4.15	Salicylic acid released from the blend films with 80% chitosan	
	content containing glutaraldehyde concentration of 0.001, 0.01,	
	and 0.5 mole/glucosamine unit at pH 2.0, 5.5 and 7.2	35
B1	FTIR spectrum of chitosan	44
C1	Reduced viscosity (η_{sp}/c) and $\ln ((\eta_{rel})/c)$ versus	
	concentration of chitosan solution	46
D1	UV spectrum of theophylline	47
D2	UV spectrum of diclofenac sodium	47
D3	UV spectrum of salicylic acid	48
D4	UV spectrum of amoxicillin trihydrate	48
D5	UV spectrum of glutaraldehyde	49
E1	Calibration curve of theophylline solution	51
E2	Calibration curve of diclofenac sodium solution	52
E3	Calibration curve of salicylic acid solution	53
E4	Calibration curve of amoxicillin trihydrate solution	54