

FORMULATION OF MICROENCAPSULATED
PARACETAMOL BEADS IN DRIED JELLY FORM FOR
PAEDIATRIC

BY

SAMAH HAMED ABDULRAHMAN ALMURISI

A thesis submitted in fulfillment of the requirement for the
degree of Doctor of Philosophy in Pharmaceutical Sciences
(Pharmaceutical Technology)

Kulliyyah of Pharmacy
International Islamic University Malaysia

MAY 2020

ABSTRACT

Taste masking is required for bitter drugs to enhance patient compliance, especially among the paediatric population. Paracetamol is a drug that exhibits bitter taste because of its chemical structure. This study aims to improve the palatability of paracetamol through using microencapsulation technique to mask the bitter taste of paracetamol and jelly dosage form to make it easy for swallowing. Paracetamol was encapsulated in alginate beads using electrospray technique to create spherically shaped beads with a diameter size of less than 1.5 mm. The alginate beads were coated with 0.3% w/v low molecular weight chitosan to provide an extra barrier for taste masking properties. The optimised paracetamol beads were 1.39 ± 0.08 mm in size and spherical with an encapsulation efficiency of $99 \pm 1.087\%$. *In vitro* studies show that the beads effectively masked the bitter taste of paracetamol. For the jelly dosage form, five different gelling agents including gelatin, three types of carrageenan namely kappa (κ)-, iota (ι)-, lambda (λ), and low acyl gellan gum were selected for the study. The jelly dosage form acts as a vehicle and eases the swallowing process. Iota-carrageenan had the best results in terms of texture, rheology and absence of syneresis. Based on this result, ι -carrageenan was modified to a dry form for reconstitution before use. The instant jelly form is more practical in terms of shipping, storage, stability and low amount of excipient used. The dry chitosan coated paracetamol alginate beads, and instant jelly was mixed to form a single dose (in sachet). Compatibility study was performed on the dosage form using differential scanning calorimetry (DSC) supported by attenuated total reflection-fourier transform infrared spectral studies (ATR-FTIR). The DSC and FTIR results showed compatibility between paracetamol and the instant jelly excipient. The optimised paracetamol jelly was easily reconstituted in 20 mL of water within 2 minutes. The beads were distributed in the jelly with no sedimentation. The time needed to release 80% of paracetamol ranged between 54-62 minutes, depending on the pH of the medium, and ingestion time was within 30 minutes after reconstitution to effectively mask the bitter taste. For the stability study, the dosages were packaged in semipermeable and impermeable sachets and stored both in real-time and accelerated stability chamber. The stability of paracetamol in the impermeable sachets, including appearance and drug content, met compendia specifications. Meanwhile, the semipermeable sachets stored in accelerated stability chamber underwent significant changes in formulation properties. The dry chitosan coated paracetamol alginate beads in jelly dosage had similar palatability and texture to commercial Panadol children's suspension and overcome the bitter aftertaste of paracetamol. Additionally, the jelly dosage form recorded low taste feeling score compared to commercial paracetamol suspension. In conclusion, the combined microencapsulation technique and jelly vehicle dosage form can replace the use of sweetening and flavouring agents in paracetamol dosage forms for the paediatric population and is comparable to commercial children's paracetamol suspension.

خلاصة البحث

إخفاء المذاق المرير للأدوية هو شرط أساسي لتحسين إمتثال المريض للدواء وخاصة الأطفال. الباراسيتامول هو أحد الأدوية التي لديها مذاق مرير بسبب تركيبته الكيميائية. الهدف من هذه الدراسة هو إخفاء الطعم المر للباراسيتامول واستكشاف قدرة الكبسلة الدقيقة والجيلي على استساغة الدواء. يتم تغليف الباراسيتامول بالألجينات عن طريق إستخدام تقنية الطلاء الكهربائي للحصول على حبيبات ألجينات مقاسها لا يتعدى ١,٥ مم و كروية الشكل. بالإضافة إلى ذلك فإن طلاء حبيبات الألجينات بالشيتوزان يوفر حاجزا إضافيًا لتعزيز إخفاء المذاق المرير للباراسيتامول. بناء على ذلك تم اختيار حبيبات الباراسيتامول المغلفة بالألجينات والمطلية ب ٠,٣% من الشيتوزان المنخفض الوزن الجزيئي وكان حجمها $1,39 \pm 0.08$ مم وكروي الشكل وكانت كفاءه التغليف $99\% \pm 1,087$, كما أنها كانت فعالة في إخفاء مذاق الباراسيتامول المر بناء على الدراسة المخبرية.علاوه على ذلك فإن هلام الجيلي يستخدم ايضا كوسيلة للمساعدة في البلع. تمت دراسة خمسة عوامل تبلور مختلفة: الجيلاتين و الكاراجينان بأنواعل الثلاثة إيوتا و كابا و لامبدا بالإضافة إلى صمغ الجيلان منخفض الأسيل, كان الأيوتا كاراجينان الأفضل من حيث الملمس وعلم الريولوجيا وغياب التآزر. بناءً على هذه النتيجة فإنه يعدّل ليكون جاف يذوب بالماء قبل الاستخدام حيث أن الجيلي الجاف يعتبر عمليا أكثر من حيث الشحن والتخزين و يحتاج سواغات أقل. بعد ذلك يتم خلط كل من حبيبات ألجينات الباراسيتامول الجافة المطلية بالشيتوزان والجيلي الجاف معًا لتكون جرعة واحدة (كيس) وتم إجراء عدة دراسات عليها بداية بدراسة التوافق بين الباراسيتامول والسواغات المستخدمة وكانت النتيجة هي التوافق بين الباراسيتامول والسواغات. من ناحية أخرى يجب التنويه بأنه يجب تناول الجيلي خلال ٣٠ دقيقة بعد التحضير لتجنب الشعور بالطعم المر. بعد ذلك تم أخذ عينات في أكياس شبه منفذة وغير منفذة وخزنها في درجة حراره الغرفه وفي إستقرار لدراسه ثبات المنتج وقد تبين من النتائج أن جميع العينات حافظت على خصائصها ولم تتغير باستثناء العينات التي حفظت في أكياس شبه منفذة و خزنت في غرفة الثبات المتسارع حيث أنها تغيرت تغيرا ملحوظا واخيرا تم إختبار إستساغة حبيبات ألجينات الباراسيتامول الجافة المطلية بالشيتوزان في الجيلي عن طريق تجربتها على الكائن الحي و تمت مقارنتها مع تعليق الباراسيتامول الأطفال التجاري (البنادول) و كانت النتيجة أن حبيبات ألجينات الباراسيتامول الجافة المطلية بالشيتوزان في الجيلي بدون إضافه محليات ونكهات تعمل على إخفاء مذاق الباراسيتامول المر و يوفر ملمسا يشابه تعليق البندول ويتفوق على تعليق البندول التجاري من ناحيه أنه لا يعطي مذاق مرعالق في الفم بعد تناوله وكذلك سجل أقل درجة شعور تذوق للباراسيتامول. كل هذا يدل على أن تقنية الكبسلة الدقيقة إلى جانب استخدام الجيلي يمكن أن تعوض استخدام عوامل التحلية والنكهة وتتغلب ايضا على المذاق المر العالق في الفم بعد تذوق الباراسيتامول و الذي لوحظ في تعليق الباراسيتامول التجاري (البنادول).

APPROVAL PAGE

The thesis of Samah Hamed Abdulrahman Almurisi has been approved by the following:

Abd Al Monem Doolaanea
Supervisor

Md.Zaidul Islam Sarker
Chairman of Supervisory Committee

Bappaditya Chatterjee
Member

Mohd Rushdi Abu Bakar
Internal Examiner

Yusrida Darwis
External Examiner

Haliza Katas
External Examiner

Suzanah Abdul Rahman
Chairperson

DECLARATION

I hereby declare that this thesis is the result of my own investigations, except where otherwise stated. I also declare that it has not been previously or concurrently submitted as a whole for any other degrees at IIUM or other institutions.

Samah Hamed Abdulrahman Almurisi

Signature Date

INTERNATIONAL ISLAMIC UNIVERSITY MALAYSIA

**DECLARATION OF COPYRIGHT AND AFFIRMATION
OF FAIR USE OF UNPUBLISHED RESEARCH**

**FORMULATION OF MICROENCAPSULATED PARACETAMOL
BEADS IN DRIED JELLY FORM FOR PAEDIATRIC**

I declare that the copyright holders of this thesis are jointly owned by the student and IIUM.

Copyright © 2020 by Samah Hamed Abdulrahman Almurisi and International Islamic University Malaysia. All rights reserved

No part of this unpublished research may be reproduced, stored in a retrieval system, or transmitted, in any form or by any means, electronic, mechanical, photocopying, recording or otherwise without prior written permission of the copyright holder except as provided below

1. Any material contained in or derived from this unpublished research may only be used by others in their writing with due acknowledgement.
2. IIUM or its library will have the right to make and transmit copies (print or electronic) for institutional and academic purposes.
3. The IIUM library will have the right to make, store in a retrieval system and supply copies of this unpublished research if requested by other universities and research libraries.

By signing this form, I acknowledged that I have read and understand the IIUM Intellectual Property Right and Commercialization policy.

Affirmed by Samah Hamed Abdulrahman Almurisi

.....
Signature

.....
Date

ACKNOWLEDGMENT

First and foremost, I would like to thank ALLAH the almighty for standing by me in the most difficult situations in my research and giving me the strength, knowledge and ability to undertake this research of study, with the help of ALLAH under whose blessing and guidance I have completed this thesis as a requirement for my PhD in Pharmaceutical Technology.

I would like to dedicate my degree to the family, especially to my father, the late Hamed Almurisi and my mother Badria Abdulrazaq for their support, motivation and courage to keep me moving forward. I would like to extend heartfelt gratitude to my siblings; Hanan, Mohammed, Layal, Abdulaziz, and Marwa who have given me effective incentive and encouragement which kept me motivated, sane and on schedule to complete this research. Without their support and pep talks, this research and thesis would not have been possible.

My deepest gratitude to my supervisor Asst. Prof. Dr Abd Almonem Doolaanea, who has given me support and encouragement, facilitated the successful completion of my work. I appreciate his detailed comments and useful suggestions which have considerably improved this thesis. My highest appreciation also goes all my all colleagues and friends Atheer, Bayan, Sarah, Asma, Anjli, Rana, Doaa and Dana for their support and encouragement during my PhD journey.

I would like to convey a very special thanks to my co-supervisor, Assoc. Prof. Dr Bappaditya Chatterjee, Pharm. Tech Department and Kulliyyah for their help in my research. I am also very thankful to Pharm Tech science officer, laboratory staff and PG friends.

TABLE OF CONTENTS

Abstract	ii
Abstract in Arabic	iii
Approval page	iv
Declaration	v
Copyright	vi
Acknowledgment	vii
Table of Contents	viii
List of Tables	xiv
List of Figures	xvii
List of Abbreviations	xxv
CHAPTER ONE INTRODUCTION	1
1.1 Background of the Study	1
1.2 Problem Statement.....	3
1.3 Hypothesis	4
1.4 Research Aim and Objectives.....	4
1.5 Research Flow	5
CHAPTER TWO LITERATURE REVIEW	8
2.1 Paediatric Dosage Form.....	8
2.2 The Drug of Interest: Paracetamol.....	11
2.3 Taste Masking Techniques	12
2.3.1 Functional Masking (Formulation Level).....	13
2.3.2 Physical Masking (Particle Level).....	14
2.3.3 Biochemical Masking (Molecular Level)	15
2.4 Selection of the Taste Masking Method	16
2.4.1 Microencapsulation Technique.....	18
2.4.1.1 Alginate (Coating Material)	18
2.4.1.2 Electrospray Technique.....	22
2.4.2 Jelly Dosage Form	24
2.4.2.1 The Gelling Agents	26
2.4.2.2 Selection of Gelling Agent.....	29
2.5 Taste Evaluation Method.....	33
2.5.1 <i>In vivo</i> Method	33
2.5.1.1 Human Taste Panel.....	33
2.5.1.2 Animal Taste Panel	35
2.5.2 <i>In vitro</i> Drug Release.....	36
2.5.3 Biomimetic Taste Sensing Systems.....	37
CHAPTER THREE CHITOSAN COATED PARACETAMOL ALGINATE BEADS	38
3.1 Introduction	38
3.2 Materials	40
3.3 Methods	40

3.3.1	Validation of UV Spectrophotometer Method for Quantification of Paracetamol	40
3.3.1.1	Preparation of Paracetamol Stock Solution.....	40
3.3.1.2	Determination of Paracetamol Max Absorbance (λ_{\max}) ..	40
3.3.1.3	Preparation of Standard Solution	41
3.3.1.4	Method Validation.....	41
3.3.2	Preparation of Paracetamol Alginate Beads	44
3.3.2.1	Statistical Optimization of Paracetamol Alginate Beads	45
3.3.3	Preparation of Chitosan Coated Paracetamol Alginate Beads.....	46
3.3.3.1	Statistical Optimization of Chitosan Coated Paracetamol Alginate Beads.....	46
3.3.4	Characterisations of Paracetamol Beads.....	48
3.3.4.1	Compatibility.....	48
3.3.4.1.1	Differential Scanning Calorimetric Analysis (DSC).....	50
3.3.4.1.2	Attenuated Total Reflection Fourier Transform Infrared (ATR-FTIR) Spectral Studies.....	50
3.3.4.2	Size and Shape of Paracetamol Beads.....	49
3.3.4.3	Determination of Encapsulation Efficiency (EE) and Drug Loading (DL).....	50
3.3.4.4	In vitro Taste Masking Evaluation	51
3.3.4.5	Swelling Studies of Optimised Paracetamol Beads	52
3.3.5	<i>In vitro</i> Release Studies of Optimised Paracetamol Beads	53
3.3.5.1	Analysis of in vitro Drug Release Kinetics and Mechanism	54
3.3.6	Statistical Analysis.....	55
3.4	Result and Discussion.....	55
3.4.1	Determination of λ_{\max}	55
3.4.2	Method Validation	56
3.4.2.1	Specificity.....	56
3.4.2.2	Linearity	57
3.4.2.3	Limit of Detection (LOD) and Limit of Quantification (LOQ)	58
3.4.2.4	Precision and Accuracy.....	60
3.4.2.5	Robustness.....	62
3.4.3	Characterisation of Paracetamol Beads	63
3.4.3.1	Compatibility Study	63
3.4.3.1.1	DSC.....	65
3.4.3.1.2	ATR-FTIR	67
3.4.3.2	The Size and Shape of Paracetamol Beads	67
3.4.3.2.1	Paracetamol Alginate Beads	69
3.4.3.2.2	Chitosan coated Paracetamol Alginate Beads ..	77
3.4.3.3	Determination of Drug Loading (DL) and Encapsulation Efficiency (EE)	76
3.4.3.4	In Vitro Taste Masking Evaluation	80
3.4.3.5	Swelling Study of Optimised Formulation.....	84

3.4.4	Drug Release Study of Optimised Paracetamol Beads	86
3.5	Conclusion	91

CHAPTER FOUR PREPARATION AND CHARACTERIZATION OF INSTANT DISSOLVING JELLY 93

4.1	Introduction	93
4.2	Materials	95
4.3	Methods	95
4.3.1	Preparation of Jellies.....	95
4.3.2	Preparation of Instant Dissolving Jelly	96
4.3.3	Characterisation	96
4.3.3.1	Physical Observation.....	96
4.3.3.2	Texture Analysis	96
4.3.3.3	Rheological Measurements	97
4.3.3.4	Compatibility.....	98
4.3.3.4.1	DSC.....	100
4.3.3.4.2	ATR-FTIR	100
4.3.3.5	Syneresis.....	98
4.3.4	Statistical Analysis.....	99
4.4	Results and Discussion	99
4.4.1	Characterisation of Gelling Agent	99
4.4.1.1	Physical Observation.....	99
4.4.1.2	Texture Profile Analysis (TPA)	100
4.4.1.2.1	Hardness	100
4.4.1.2.2	Cohesiveness.....	100
4.4.1.2.3	Adhesiveness	100
4.4.1.2.4	Gumminess	100
4.4.1.3	Rheology Measurements	106
4.4.1.3.1	Flow Behaviour of Gelling Agents.....	100
4.4.1.3.2	Stress Sweep Test	100
4.4.1.4	Syneresis.....	123
4.4.2	Instant Dissolving Jelly.....	123
4.4.3	Characterisations of Optimised Instant Jelly	128
4.4.3.1	Compatibility Study	128
4.4.3.2	Reconstitution Time and Physical Observation	130
4.4.3.3	Texture Profile Analysis (TPA)	130
4.4.3.4	Rheology of Instant Jelly.....	131
4.4.3.5	Syneresis.....	133
4.5	Conclusion	133

CHAPTER FIVE FORMULATION OF PARACETAMOL INSTANT DISSOLVING JELLY DOSAGE FORM 134

5.1	Introduction	134
5.2	Materials	135
5.3	Methods	136
5.3.1	Preparation of Dry Chitosan Coated Paracetamol Alginate Beads	136
5.3.2	Preparation of Dry Instant Dissolving Jelly.....	136

5.3.3	Preparation of Dry Chitosan Coated Paracetamol Alginate Beads in Instant Jelly (Paracetamol Jelly)	136
5.3.4	Characterisations of Paracetamol Jelly	137
5.3.4.1	Compatibility Study	137
5.3.4.1.1	Differential Scanning Calorimetric Analysis (DSC).....	137
5.3.4.1.2	Fourier Transform Infrared Spectral Studies (ATR-FTIR).....	137
5.3.4.1.2	Moisture Content	138
5.3.4.2	Drug Content	138
5.3.4.3	Reconstitution Time and Physical Observation	138
5.3.4.4	Texture Profile Analysis.....	138
5.3.4.5	Rheological Measurements	139
5.3.4.6	Determination of Free Paracetamol in Jelly	139
5.3.4.7	In vitro Release Studies	139
5.3.5	Statistical Analysis.....	141
5.4	Results and Discussion	142
5.4.1	Dry Chitosan Coated Paracetamol Alginate Beads in Instant Jelly (Paracetamol Jelly) Packed in Sachet.....	142
5.4.2	Compatibility Study	142
5.4.2.1	DSC	142
5.4.2.2	ATR-FTIR.....	143
5.4.3	Moisture Content	144
5.4.4	Drug Content.....	146
5.4.5	Reconstitution Time and Physical Observation.....	146
5.4.6	Texture Profile Analysis	147
5.4.7	Rheological Measurements.....	148
5.4.8	Determination of Free Paracetamol in the Jelly.....	150
5.4.9	<i>In vitro</i> Release Study	151
5.5	Conclusion	159

CHAPTER SIX STABILITY STUDY 161

6.1	Introduction	161
6.2	Materials	163
6.3	Methods	163
6.3.1	Instruments and Chromatographic Conditions	163
6.3.1.1	Standard Solutions.....	164
6.3.1.1.1	Solution of Paracetamol.....	164
6.3.1.1.2	Solution of Paracetamol Jelly	164
6.3.1.2	Method Validation.....	165
6.3.1.2.1	System Suitability	165
6.3.1.2.2	Specificity	165
6.3.1.2.3	Force Degradation Studies.....	165
6.3.1.2.4	Linearity, Limit of Detection (LOD) and Limit of Quantification (LOQ).....	165
6.3.1.2.5	Accuracy and Precision	165
6.3.2	Stability Study.....	168
6.3.2.1	Physical observation.....	168
6.3.2.2	Moisture Content.....	169

6.3.2.3	Reconstitution Time	169
6.3.2.4	Texture Profile Analysis.....	169
6.3.2.5	Rheology measurement	169
6.3.2.6	Determination of Free Paracetamol in the Jelly	169
6.3.2.7	Determination of Drug content	170
6.3.2.8	In vitro Drug Release	170
6.3.3	Statistical Analysis.....	170
6.4	Results and Discussion	171
6.4.1	HPLC Method for quantification of paracetamol	171
6.4.1.1	System Suitability	171
6.4.1.2	Specificity.....	172
6.4.1.3	Force Degradation of Paracetamol.....	173
6.4.1.4	Linearity, LOD, and LOQ.....	176
6.4.1.5	Precision and Accuracy.....	176
6.4.2	Stability	177
6.4.2.1	Physical Observation.....	177
6.4.2.2	Moisture Content.....	178
6.4.2.3	Reconstitution Time	180
6.4.2.4	Texture Analysis	180
6.4.2.5	Rheological Measurements	182
6.4.2.6	Determination of Free Paracetamol in the Jelly	185
6.4.2.7	Paracetamol Content	188
6.4.2.8	In vitro Drug Release	194
6.5	Conclusion.....	197

CHAPTER SEVEN TASTE MASKING EFFICACY OF PARACETAMOL ORAL JELLY 198

7.1	Introduction	198
7.2	Materials	200
7.3	Methods	200
7.3.1.....	Preparation of Chitosan Coated Paracetamol Alginate Beads	200
7.3.2	Preparation of Instant Dissolving Jelly.....	201
7.3.3	<i>In vivo</i> Taste Masking Assessment.....	201
7.3.3.1	Study Design	201
7.3.3.2	Sample Size.....	201
7.3.3.3	Human Subject Selection Criteria.....	202
7.3.3.4	Determining the Threshold Concentration of Paracetamol	202
7.3.3.5	Palatability Test.....	203
7.3.4	Statistical Analysis.....	204
7.4	Results and Discussion	205
7.4.1	Threshold Concentration of Paracetamol	205
7.4.2	Palatability Test	205
7.4.2.1	Smell.....	205
7.4.2.2	Taste	206
7.4.2.3	Taste masking.....	207
7.4.2.4	Texture	208
7.4.2.5	Aftertaste	209

7.4.2.6 Taste Feeling Score	210
7.5 Conclusion	211
CHAPTER EIGHT CONCLUSION AND FUTURE WORK.....	213
8.1 General Conclusion	213
8.2 Recommendation And Future Works	216
REFERENCES.....	217
APPENDIX I: ETHICAL APPROVAL	252
APPENDIX II: RESEARCH ACHIEVEMENTS	253
APPENDIX III: APPROVED READING.....	256

LIST OF TABLES

Table No.		Page No.
3.1	Independent & dependent variables of electrospray	47
3.2	Independent & dependent variables of chitosan coating and their levels	49
3.3	Independent & dependent variables and levels used for encapsulation efficiency (EE)	49
3.4	LOD, LOQ, and % RSD in different buffers	61
3.5	Precision study of paracetamol QC samples in HCl pH 1.2 & acetate buffers pH 4.5	62
3.6	Precision study of paracetamol QC samples in phosphate buffer pH 5.8 & pH 6.8	62
3.7	Accuracy study of paracetamol in HCl pH 1.2 & acetate buffers pH 4.5	63
3.8	Accuracy study of paracetamol in phosphate buffer pH 5.8 & pH 6.8	63
3.9	Absorbances of pure paracetamol (conc. 10 µg/mL) at 3 consecutive wavelengths in HCl pH 1.2 & acetate buffers pH 4.5	64
3.10	Absorbances of paracetamol (conc. 10 µg/mL) at 3 consecutive wavelengths in phosphate buffer pH 5.8 & pH 6.8	64
3.11	Effect of chitosan coating on the size of paracetamol alginate beads prepared at 6 kV in wet beads and at 4 kV in dry beads	78
3.12	Impact of high and low MW of chitosan on EE and DL. Mean ± SD, n = 3	81
3.14	Regression coefficients of different mathematical models	92
3.15	Time (min) necessary to release 25, 50, 75, 80 and 90% of paracetamol loaded in chitosan coated alginate beads at different media. Mean ± SD, n=3.	93

4.1	Physical observations of different gelling agents and their concentrations	103
4.2	The parameters (r , n , K), and η_{app} at 50 s ⁻¹ obtained by the power-law model	114
4.3	Results of stress sweep test for different hydrocolloids.	124
5.1	Paracetamol instant jelly formulation.	139
5.2	Time (min) needed to release 25, 50, 75, 80 and 90% of paracetamol loaded in chitosan coated alginate beads in jelly at different media. Mean \pm SD, $n = 3$.	158
5.3	Time (min) needed to release 50% of paracetamol in F1: chitosan coated paracetamol alginate beads in jelly, F2: chitosan coated paracetamol alginate beads, F3: Panadol Children's Suspension, F4: Panadol Chewable Tablets for Children in different media. Mean \pm SD, $n = 3$.	159
5.4	Similarity factor (f_2) of F1: chitosan coated paracetamol alginate beads in jelly, F2: chitosan coated paracetamol alginate beads, F3: Panadol Children's Suspension, F4: Panadol Chewable Tablets for Children in different media	160
5.5	The dissolution efficiency (DE) of F1: chitosan coated paracetamol alginate beads in jelly, F2: chitosan coated paracetamol alginate beads, F3: Panadol Children's Suspension, F4: Panadol Chewable Tablets for Children in different media	161
6.1	System Suitability Testing ($n=6$)	173
6.2	Results from analysis of standard and sample from the forced degradation study	176
6.3	Precision and accuracy of paracetamol jelly at intra and inter-day	179
6.4	The physical appearance of paracetamol jelly powder after storage in semi-permeable sachets at different time points (0, 2 weeks, 1, 2, and 3 months)	180
6.5	The physical appearance of paracetamol jelly powder after storage in impermeable sachets at different time points (0, 2 weeks, 1, 2, and 3 months)	180
6.6	The moisture content of paracetamol jelly powder after storage in semi-permeable sachets at different time points (0, 2 weeks, 1, 2, and 3 months)	181
6.7	The moisture content of sachet after storage in impermeable	

	sachets at different time points (0, 2 weeks, 1, 2, and 3 months)	182
6.8	The texture profile analysis (TPA) of paracetamol jelly stored in semi-permeable sachets at different time points (0, 2 weeks, 1, 2, and 3 months)	183
6.9	The texture profile analysis (TPA) of paracetamol jelly stored in impermeable sachets at different time points (0, 2 weeks, 1, 2, and 3 months)	183
6.10	The paracetamol content of paracetamol jelly after storage in semi-permeable sachets at different time points (0, 2 weeks, 1, 2, and 3 months)	191
6.11	The paracetamol content of paracetamol jelly after storage in impermeable sachets at different time points (0, 2 weeks, 1, 2, and 3 months)	191
6.12	Degradation rate constants and shelf life of sachets determined at various temperatures and packaging system	196

LIST OF FIGURES

<u>Figure No.</u>		<u>Page No.</u>
1.1	Research flow	7
2.1	Chemical structure of Paracetamol	11
2.2	Types of taste masking techniques to improve the acceptability of patients	13
2.3	Chemical structural of alginates: G-block, M-block, and alternating block in alginate	19
2.4	Crosslinking reaction between sodium alginate and calcium	20
2.5	Preparation of chitosan coated calcium alginate beads	22
2.6	Drug release mechanisms of microcapsules system	23
2.7	Schematic representation of electrospray setup	24
2.8	Chemical structure of various types of carrageenan	28
2.9	Chemical structure of low acyle gellan gum	29
2.10	Basic chemical structure of gelatin	29
2.11	Flow behaviour (viscosity vs. shear rate)	32
2.12	Stress sweep test graph	34
2.13	<i>In vitro</i> taste masking method	38
3.1	Electrospray apparatus using for paracetamol beads	47
3.2	Flow chart of image processing procedures of paracetamol beads image	51
3.3	Instrument used in evaluating <i>in vitro</i> taste masking method	54
3.4	Spectra of pure paracetamol 5, 10, 15, & 20 µg/mL	58
3.5	Spectrums of pure paracetamol, paracetamol beads, and placebo	59
3.6	Standard curves of paracetamol in different buffers	60

3.7	Low concentration calibration curves of paracetamol (0.1-0.5 µg/mL) in in different buffers	61
3.8	DSC curves of alginate, chitosan, blank beads, and chitosan coated paracetamol alginate beads	66
3.9	ATR-FTIR spectrums of (a) Alginate, (b) Chitosan, (c) Blank beads, (d) Paracetamol, and (f) Chitosan coated paracetamol alginate beads	69
3.10	Tear-shaped beads prepared using 3% w/v of sodium alginate	70
3.11	The main effect of electrical voltage and flow rate on bead size	71
3.12	The interaction effect of electrical voltage and flow rate on bead size	73
3.13	The main effect of electrical voltage and flow rate on bead shape	73
3.14	The interaction Effect of electrical voltage and flow rate on bead shape	73
3.15	2-Dimensional contour plots of beads size	74
3.16	2-Dimensional contour plots of beads shape	75
3.17	The size of paracetamol alginate beads measured using optical microscopy, 5 × 10 (a, b and C) wet beads, (d, e and f) dry beads prepared at different electrical voltages	76
3.18	The Morphology of paracetamol alginate beads coated with 0.3% w/v high MW chitosan as a) wet bead prepared by 6 kV and b) dry bead prepared by 4 kV	77
3.19	Effect of (a) pH of gelation path, and (b) gelation time on encapsulation efficiency (EE%)	79
3.20	Comparison of paracetamol release from wet paracetamol alginate beads prepared at different electrical voltages. Mean ± SD, n = 3	83
3.21	Comparison of paracetamol release from dry paracetamol alginate beads prepared at different electrical voltages. Mean ± SD, n = 3	83
3.22	Comparison of paracetamol release from wet paracetamol alginate beads coated using different concentrations of low and high MW chitosan. Mean ± SD, n = 3	85
3.23	Comparison of paracetamol release from dry paracetamol alginate beads coated using different concentrations of low and high MW chitosan. Mean ± SD, n = 3	85

3.24	Time-lapse microphotographs of paracetamol alginate beads coated with 0.3% low MW chitosan (a) HCl buffer pH 1.2 (b) acetate buffer pH 4.5 (c) phosphate buffer pH 5.8 (d) phosphate buffer pH 6.8 taken using an optical microscope	87
3.25	Comparison of swelling profiles of paracetamol alginate beads coated with low MW chitosan in HCl, acetate and phosphate buffer. Mean \pm SD, n = 3	87
3.26	Comparison of paracetamol releases of dry chitosan coated paracetamol alginate beads in different media. Mean \pm SD, n = 3	89
3.27	Comparison of dissolutions media image after <i>in vitro</i> release of chitosan coated paracetamol alginate beads the test a) at pH 1.2 or pH 4.8 and b) at pH 5.8 or pH 6.8	89
3.28	Release of dry chitosan coated paracetamol alginate beads in HCl buffer pH1.2 (2h) and phosphate buffer pH 6.8 (2h).	91
4.1	Hardness of the gelling agents and commercial products. Mean \pm SD, (n = 3). Similar letters denote no significant difference (ANOVA, <i>p</i> -value > 0.05)	104
4.2	Cohesiveness of the gelling agents and commercial products. Mean \pm SD, (n = 3). Similar letters denote no significant difference (ANOVA, <i>p</i> -value > 0.05).	105
4.3	Adhesiveness of the gelling agents and commercial products. Mean \pm SD, (n = 3). Similar letters denote no significant difference (ANOVA, <i>p</i> -value > 0.05).	106
4.4	Gumminess of the gelling agents and commercial products. Mean \pm SD, (n = 3). Similar letters denote no significant difference (ANOVA, <i>p</i> -value > 0.05).	107
4.5	Flow curve of gelatin 8%, 9 % and 10% w/v	112
4.6	Flow curve of iota-carrageenan 1%, 2%, and 3% w/v	112
4.7	Flow curve of kappa-carrageenan 3%, 4% and 5% w/v	113
4.8	Flow curve of lambda- carrageenan 3%, 4 %, and 5% w/v	113
4.9	Flow curve of kelogel F 1%, 1.5 %, and 2% w/v	114
4.10	Stress sweep test of gelatin 8% (w/v): G', G'', and tan δ	117
4.11	Stress sweep test of gelatin 9% (w/v): G', G'', and tan δ	117

4.12	Stress sweep test of gelatin 10% (w/v): G' , G'' , and $\tan \delta$	118
4.13	Stress sweep test of ι -carrageenan 1 % (w/v): G' , G'' , and $\tan \delta$	118
4.14	Stress sweep test of ι -carrageenan 2% (w/v): G' , G'' , and $\tan \delta$	119
4.15	Stress sweep test of ι -carrageenan 3% (w/v): G' , G'' , and $\tan \delta$	119
4.16	Stress sweep test of κ -carrageenan 3% (w/v): G' , G'' , and $\tan \delta$	120
4.17	Stress sweep test of κ -carrageenan 4% (w/v): G' , G'' , and $\tan \delta$	120
4.18	Stress sweep test of κ -carrageenan 5% (w/v): G' , G'' , and $\tan \delta$	121
4.19	Stress sweep test of λ -carrageenan 3% (w/v): G' , G'' , and $\tan \delta$	121
4.20	Stress sweep test of λ -carrageenan 4% (w/v): G' , G'' , and $\tan \delta$	122
4.21	Stress sweep test of λ -carrageenan 5% (w/v): G' , G'' , and $\tan \delta$	122
4.22	Stress sweep test of Kelogel F 1% (w/v): G' , G'' , and $\tan \delta$	123
4.23	Stress sweep test of Kelogel F 1.5% (w/v): G' , G'' , and $\tan \delta$	123
4.24	Stress sweep test of Kelogel F 2% (w/v): G' , G'' , and $\tan \delta$	124
4.25	The physical observation of jelly formulation (FJ1) when dispersed in water	126
4.26	The physical observation of jelly formulation (FJ1) when dispersed in water after grinding and sieving	126
4.27	The freeze-dried jelly formulation (FJ1) a) initially, and b) when dispersed in water.	127
4.28	The physical observation of jelly formulation (FJ2) when dispersed in water	129
4.29	The physical observation of optimised instant jelly (FJ3)	130
4.30	DSC scan of glycine, iota-carrageenan, calcium lactate gluconate, and instant jelly powder	131
4.31	ATR-FTIR spectrums of (a) glycine, (b) iota-carrageenan, (c) calcium lactate gluconate, and (d) instant jelly powder	132
4.32	Flow curve of instant dissolving jelly	134

4.33	Stress sweep test of instance dissolving jelly: G' , G'' , and $\tan \delta$	134
5.1	Paracetamol instant jelly packed in a sachet	144
5.2	DSC thermogram of instant jelly powder, dry chitosan coated paracetamol alginate beads in instant jelly, and chitosan coated paracetamol alginate beads	145
5.3	ATR-FTIR spectrums of (a) chitosan coated paracetamol alginate beads (b) instant jelly powder and (c) chitosan-coated paracetamol alginate beads in jelly	146
5.4	Dispersion of dry chitosan coated paracetamol alginate beads in jelly	149
5.5	Texture profile analysis (TPA) of paracetamol instant jelly and marketed products; (a) hardness, (b) cohesiveness, (c) adhesiveness, and (d) gumminess. Mean \pm SD, n = 3	150
5.6	Flow curve of dry chitosan coated paracetamol alginate beads in jelly	151
5.7	Stress sweep test of dry chitosan coated paracetamol alginate beads in jelly: G' , G'' , and $\tan \delta$	152
5.8	Release of paracetamol from dry chitosan coated alginate beads to the jelly vehicle. Mean \pm SD, n = 3	153
5.9	Comparison of paracetamol release from F1(chitosan coated paracetamol alginate beads in jelly), F2 (chitosan coated paracetamol alginate beads), F3 (Panadol Children's Suspension), F4 (Panadol Chewable Tablets for Children) in HCl buffer pH1.2 media. Mean \pm SD, n = 3	155
5.10	Comparison of paracetamol release from F1(chitosan coated paracetamol alginate beads in jelly), F2 (chitosan coated paracetamol alginate beads), F3 (Panadol Children's Suspension), F4 (Panadol Chewable Tablets for Children) in acetate buffer pH 4.5 media. Mean \pm SD, n = 3	155
5.11	Comparison of paracetamol release from F1(chitosan coated paracetamol alginate beads in jelly), F2 (chitosan coated paracetamol alginate beads), F3 (Panadol Children's Suspension), F4 (Panadol Chewable Tablets for Children) in phosphate buffer pH 5.8 media. Mean \pm SD, n = 3	155
5.12	Comparison of paracetamol release from F1(chitosan coated paracetamol alginate beads in jelly), F2 (chitosan coated paracetamol alginate beads), F3 (Panadol Children's Suspension),	

	F4 (Panadol Chewable Tablets for Children) in phosphate buffer pH 6.8 media. Mean \pm SD, n = 3	156
5.13	Comparison of paracetamol release from F1(chitosan coated paracetamol alginate beads in jelly), F2 (chitosan coated paracetamol alginate beads), F3 (Panadol Children's Suspension), F4 (Panadol Chewable Tablets for Children) in in HCl buffer pH1.2 (2 h) and phosphate buffer pH 6.8 (2 h). Mean \pm SD, n = 3	156
6.1	The chromatogram of paracetamol standard solution (0.01 mg/ml) with 6 replicated for a system suitability test	174
6.2	Chromatograms of blank (Data 1), placebo (Data 2), standard (Data 3), and sample (Data 4)	175
6.3	Chromatograms of standard and sample at the control and after force degradation	177
6.4	Standard curve of linearity for paracetamol	178
6.5	The flow curve of semi-permeable sachet stored in real time chamber at different time points (0, 2 weeks, 1, 2, and 3 months).	185
6.6	The flow curve of semi-permeable sachets stored in accelerated stability chamber at different time points (0, 2 weeks, 1, 2, and 3 months)	185
6.7	The flow curve of impermeable sachets stored in real time stability chamber at different time points (0, 2 weeks, 1, 2, and 3 months)	186
6.8	The flow curve of impermeable sachets stored in accelerated stability chambers at different time points (0, 2 weeks, 1, 2, and 3 months)	186
6.9	The appearance of jelly: a) at 0 time point, and b) after stored in a semi-permeable sachets in accelerated chamber at 3 month	187
6.10	Release of paracetamol from dry chitosan coated alginate beads to jelly vehicle after storage in semi-permeable sachets in real time stability at different time points (0, 2 weeks, 1, 2, and 3 months)	188
6.11	Release of paracetamol from dry chitosan coated alginate beads to jelly vehicle after storage in semi-permeable sachets in accelerated stability at different time points (0, 2 weeks, 1, 2, and 3 months)	189
6.12	Release of paracetamol from dry chitosan coated alginate beads to jelly vehicle after storage in impermeable sachets in real time stability at different time points (0, 2weeks, 1, 2, and 3month)	189

6.13	Release of paracetamol from dry chitosan coated alginate beads to the jelly vehicle after storage in impermeable sachets in accelerated stability at different time points (0, 2 weeks, 1, 2, and 3 months)	190
6.14	The regression line for the remaining % of the paracetamol stored in semi-permeable sachets at real time and accelerated storage temperature against time (zero order).	193
6.15	The regression line of the logarithm of the remaining % of the paracetamol in semi-permeable sachets at real time and accelerated storage temperature against time (first order)	193
6.16	The regression line for the remaining % of the paracetamol stored in impermeable sachets at real time and accelerated storage temperature concentration against time (zero order)	194
6.17	The regression line of the logarithm of the remaining % of paracetamol stored in impermeable sachets at real time and accelerated storage temperature against time (first order)	194
6.18	<i>In vitro</i> drug release in phosphate buffer pH 5.8 after storage in semi-permeable sachets in real time stability at different time points (0, 2 weeks, 1, 2, and 3 months)	197
6.19	<i>In vitro</i> drug release in phosphate buffer pH 5.8 after storage in semi-permeable sachets in accelerated stability at different time points (0, 2 weeks, 1, 2, and 3 months)	197
6.20	<i>In vitro</i> drug release in phosphate buffer pH 5.8 after storage in impermeable sachets in real time stability at different time points (0, 2 weeks, 1, 2, and 3 months)	198
6.21	<i>In vitro</i> drug release in phosphate buffer pH 5.8 after storage in impermeable sachets in accelerated stability at different time points (0, 2 weeks, 1, 2, and 3 months)	198
7.1	Smell score of different products based on Kruskal–Wallis tests (Median \pm SD). Error bar represents the maximum and minimum score	208
7.2	Value plots for the taste of different products based on Kruskal–Wallis tests (Median \pm SD). Error bar represents the maximum and minimum score	209
7.3	Value plots for taste masking of different products based on Kruskal–Wallis tests (Median \pm SD). Error bar represents the maximum and minimum score	211
7.4	Value plots for the texture of different products based on Kruskal–	

	Wallis tests (Median \pm SD). Error bar represents the maximum and minimum score	212
7.5	Value plots for aftertaste of different products based on Kruskal–Wallis tests (Median \pm SD). Error bar represents the maximum and minimum score	213
7.6	Value plots for taste felling score of different products based on Kruskal-Wallis tests (Median \pm SD). Error bar represents the maximum and minimum score	214