



CHARACTERIZATION OF
PALM OLEIN-IN-WATER EMULSION AS A
VEHICLE FOR TOPICAL DRUG DELIVERY OF
BETAMETHASONE 17-VALERATE

BY

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ABSTRACT

Palm olein, the major commodity of Malaysia, is inexhaustible and contains natural surfactants with the potential to be used widely in pharmaceutical formulations. However, there is little data available on the use of palm olein as an alternative in the production of topical products. The current study aims to produce pharmaceutical formulation using palm olein as the oil phase with betamethasone 17-valerate as the active ingredient and to compare the characteristics with those of commercial products. The emulsions were prepared using Span[®] 20 and Tween[®] 20 as surfactants, Carbopol[®] 940 as thickener, methyl paraben sodium, propyl paraben sodium and chlorocresol as preservatives, propylene glycol as solubilizer and distilled water as the aqueous phase. The formulations were characterised for particle size distribution, microscopic examination, viscosity, rheology, phase separation, pH and zeta potential. Evaluation on drug release with three different viscosities was further performed with Hanson Verticle Diffusion Cell System using cellulose acetate as well as rat skin as membranes and the samples were quantified with HPLC. The results were compared with that of three commercially available products which were Betnovate, Betasone and Axcel Betamethasone creams. The creams stabilized with 0.3% (w/w) of Carbopol[®] 940 were further tested for microbial limit studies according to the monographs stated in the British Pharmacopoeia (2009). The creams were further subjected to stability studies for 3 months at three different temperatures (4°C, 25°C and 40°C) and degradation of betamethasone 17-valerate in the formulations was analysed using HPLC. The formulations showed mean particle size between 2 to 4 µm, viscosity 50 to 250 mPa.s, pH 5 to 5.9 and zeta potential -45 to -68 mV. The emulsions exhibited pseudoplastic behaviour with yield stress and found to be thixotropic. The drug release rates from palm-olein-in-water emulsions were up to 4.5 times higher than that of commercial products. Less than 5 % of drug was degraded in the formulations during the 3-month period when they were subjected to three different temperatures. In conclusion, these findings proved that the creams produced from palm-olein-in-water emulsion could be a superior alternative vehicle for topical drug delivery system.

خلاصة البحث

يعد زيت النخيل البضاعة الرئيسية في ماليزيا وهو يوجد بوفرة عالية ويحتوي على عوامل طبيعية فعالة على السطح والتي من الممكن استخدامها في المستحضرات الصيدلانية. على كل حال هناك القليل من المعلومات حول استخدام زيت النخيل كبديل في المستحضرات الموضعية. تهدف الدراسة الحالية الى انتاج مستحضرات صيدلانية باستخدام زيت النخيل كطور زيتي ومادة البيتاميتازون فاليروات كمادة فعالة وتهدف أيضا الى مقارنة هذا الشكل الجديد بالأشكال المتوفرة في الاسواق. تم انتاج المستحضر باستخدام التوين 20 والسبان 20 كعوامل فعالة على السطح و الكاربوبول 940 كرافع قوام والصوديوم ميتيل بارابين والصوديوم بروبييل بارابين والكلوروكريزول كمواد حافظة وكذلك تم استخدام البروبيلين غليكول كمثبت والماء للطور المائي. تم فحص وتوصيف التحضيرات من جهة توزيع حجم الجزيئات والفحص المجهرى والزوجة و الجريان و فصل الاطوار ودرجة الحموضة و كمون بيتا. تم تقييم تحرر الدواء عند ثلاث مستويات لزوجة مختلفة باستخدام نظام خلية الحلول Hanson Verticle وأغشية السللوز اسيتات و بشرة الجرذان وتم معايرة التراكيز باستخدام الكروماتوغرافيا السائلة عالية الانجاز. لقد تمت مقارنة النتائج مع ثلاث أشكال صيدلانية متوفرة في الأسواق وهي Betnovate, Betasone و Axcel . وقد تمت دراسة حدود النمو الميكروبي للتحضيرات المستحضرة مع 0.3% من الكاربوبول طبقا لدستور الادوية البريطاني. درست ثباتية الكريم لمدة ثلاثة اشهر في ثلاث درجات حرارة مختلفة (4°C, 25°C and 40°C) وتم مراقبة تحرب البيتاميتازون باستخدام ال HPLC . أظهرت النتائج أن متوسط الحجم الجزيئي تراوح بين 2-4 ميكروميتر والزوجة بين 50-250 ميلي ثانية باسكال أما درجة الحموضة فقد تراوحت بين 5-5.9 وكمون زيتا بين 45- و 68 ميلي فولط. أبدت المستحلبات سلوكا بلاستيكيًا كاذبا كنتيجة للشد ووجد أنها متميعة بالهز. كانت مستويات تحرر الدواء من مستحلبات زيت النخيل في الماء أعلى ب 4.5 مرة من مثيلاتها المتوفرة في الأسواق. أبدت دراسة الثباتية أن أقل من 5% من الدواء تحربت بعد تعريضها لدرجات حرارة مختلفة لمدة 3 اشهر. في الخاتمة فقد برهنت النتائج أن الكريمات المنتجة من مستحلبات زيت النخيل في الماء يمكن أن تكون بديلا عظيما كحامل في أنظمة الاعطاء الدوائي الموضعي.

APPROVAL PAGE

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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.

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BETAMETHASONE 17-VALERATE**

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TABLE OF CONTENTS

Abstract	ii
Abstract in Arabic	iii
Approval Page	iv
Declaration Page	v
Copyright Page.....	vi
Acknowledgements	vii
List of Tables	xiii
List of Figures	xvi
List of Equations	xxii
List of Symbols	xxiii
List of Abbreviations	xxiv
CHAPTER ONE: INTRODUCTION	1
1.1 The Skin.....	1
1.1.1 The Skin as a Route of Drug Administration.....	4
1.2 Research Question	8
1.2.1 Statement of Problem.....	8
1.2.2 Significance of the Study	9
1.3 Aim of the Study.....	9
1.4 Scope of the Study	10
CHAPTER TWO: CHARACTERIZATION OF BETAMETHASONE 17- VALERATE FORMULATIONS PREPARED FROM PALM-OLEIN-IN- WATER EMULSIONS	11
2.1 Introduction.....	11
2.1.1 The use of palm olein as the oil phase	11
2.1.2 Surfactants.....	13
2.1.3 Viscosity inducer.....	15
2.1.4 Preservatives	16
2.1.4.1 Methyl paraben sodium	18
2.1.4.2 Propyl paraben sodium	19
2.1.4.3 Chlorocresol	20
2.1.5 Solubilizer	20
2.1.6 Betamethasone 17-valerate	21
2.2 Materials and Methods	23
2.2.1 Oil.....	23
2.2.2 Required chemicals	23
2.2.3 Evaluation of purity of betamethasone 17-valerate by DSC.....	24
2.2.4 Solubility measurements of betamethasone 17-valerate in vehicle components and receptor medium	24
2.2.4.1 Drug content analysis by spectrophotometric method	25
2.2.4.2 Preparation of standard solutions for calibration curve.....	25
2.2.5 Formulation of betamethasone 17-valerate creams and lotions.....	26
2.2.5.1 Preparation of 1% (w/w) Carbopol [®] 940 stock solution.....	26
2.2.5.2 Preparation of betamethasone 17-valerate slurry	26

2.2.5.3 Preparation of 20% (w/w) palm-olein-in-water emulsions ...	26
2.2.5.4 Preparation of betamethasone 17-valerate creams and lotions	
.....	27
2.2.6 Characterization	29
2.2.6.1 Phase Separation.....	29
2.2.6.2 Determination of particle size	30
2.2.6.3 Microscopic examination of betamethasone 17-valerate	
emulsions	31
2.2.6.4 Determination of Rheological Properties	31
2.2.6.4.1 Viscosity Measurement.....	31
2.2.6.4.2 Rheological Measurement	32
2.2.7 Performing pH Measurement and Zeta Potential Measurement	33
2.2.8 Evaluation of hydration and moisturization of rat skin by test	
emulsions	34
2.2.8.1 Experimental animals	34
2.2.8.2 Performing skin hydration test	35
2.2.9 Statistical Analysis	35
2.3 Results and discussion	36
2.3.1 Purity of betamethasone 17-valerate by DSC	36
2.3.2 Solubility measurements	36
2.3.3 Characterization	39
2.3.3.1 Phase Separation.....	39
2.3.3.2 Droplet size measurement	41
2.3.3.2.1 Effect of Carbopol® on oil droplet size.....	44
2.3.3.2.2 Effect of betamethasone 17-valerate on oil droplet size	
.....	47
2.3.3.2.3 Effect of type, concentration and HLB of	
Span®20/Tween® mixture on oil droplet size	47
2.3.3.2.4 Effect of homogenisation duration on oil droplet size	
.....	48
2.3.3.3 Microscopic examination of oil droplets.....	49
2.3.3.4 Viscosity measurements	51
2.3.3.5 Yield stress	53
2.3.3.6 Rheological measurements	54
2.3.3.6.1 Viscosity, yield stress and thixotropy	54
2.3.3.6.2 Viscoelastic properties	58
2.3.3.7 Zeta potential and pH measurements	63
2.3.4 Skin hydration test	66
2.4 Conclusion	68

CHAPTER THREE: DETERMINATION OF THE *IN VITRO* DRUG RELEASE STUDIES AND SKIN PERMEATION STUDIES OF BETAMETHASONE 17-VALERATE EMULSIONS 69

3.1 Introduction.....	69
3.1.1 The amount of drug applied in donor chamber.....	71
3.1.2 Types of membranes used in the <i>in vitro</i> drug release studies.....	73
3.1.2.1 Natural membranes.....	73
3.1.2.2 Types of natural membranes	73
3.1.2.2.1 Human skins.....	73
3.1.2.2.2 Animal skins	75

3.1.2.3 Factors affecting drug permeation across the stratum corneum	77
3.1.2.3.1 The effects of vehicles on the skin.....	77
3.1.2.4 Possible pathway of drug penetration into stratum corneum	78
3.1.2.5 The mechanism of drug diffusion across stratum corneum...	80
3.1.2.6 The fate of betamethasone 17-valerate after permeation into the skin.....	81
3.1.2.7 Synthetic membranes.....	84
3.1.2.8 Types of synthetic membranes	84
3.1.2.8.1 Synthetic membranes used for skin simulation	85
3.1.2.8.2 Synthetic membranes used for quality assessment	86
3.1.2.8.2.1 Cellulosic group	87
3.1.2.8.2.2 Polymeric group	88
3.1.2.8.3 Physicochemical properties of cellulose acetate membrane	88
3.1.2.8.4 Mechanism of diffusion across membranes.....	91
3.1.3 Receptor medium	93
3.1.4 Objective of the Chapter	95
3.2 Materials and Methods	96
3.2.1 Test products	96
3.2.2 Commercial products	96
3.2.3 Preparation of receptor medium.....	98
3.2.3.1 Deaeration of the receptor medium	99
3.2.4 <i>In vitro</i> drug release using cellulose acetate membrane.....	100
3.2.4.1 Membrane preparation.....	100
3.2.4.2 Experimental conditions.....	100
3.2.4.3 Design of the Rate Comparison Study	101
3.2.4.4 <i>In vitro</i> diffusion using cellulose acetate membrane	102
3.2.5 <i>In vitro</i> skin permeation using rat skin.....	103
3.2.5.1 Preparation of the rat skin.....	103
3.2.5.2 Skin assay: Estimation of drug content in the skin.....	104
3.2.6 Drug content analysis by HPLC.....	105
3.2.6.1 Apparatus.....	105
3.2.6.2 Reagents and chemicals.....	105
3.2.6.3 Chromatographic conditions	106
3.2.6.4 Preparation of standard solutions for calibration curve.....	106
3.2.7 Calculation of the cumulative amount release	107
3.2.8 Calculation for estimation of drug content in the skin.....	108
3.3 Results and Discussion	108
3.3.1 <i>In vitro</i> drug release of betamethasone 17-valerate using cellulose acetate membrane.....	109
3.3.1.1 Factor affecting the diffusion of betamethasone 17-valerate across cellulose acetate membrane	112
3.3.1.1.1 The effect of particle size and viscosity on drug permeation.....	112
3.3.1.1.2 The influence of physicochemical properties of membrane on drug diffusion.....	113

3.3.1.1.3 The influence of receptor medium on diffusion of betamethasone 17-valerate across cellulose acetate membrane	113
3.3.2 Results for the <i>in vitro</i> skin permeation studies of betamethasone 17-valerate using rat skin.....	114
3.3.2.1.2 Hydration	119
3.3.2.1.3 Occlusion	120
3.4 Conclusion	122

CHAPTER FOUR: MICROBIAL LIMIT STUDIES OF BETAMETHASONE 17-VALERATE CREAM..... 124

4.1 Introduction.....	124
4.1.1 Total Aerobic Microbial Count (TAMC) and Total Combined Yeasts and Moulds Count (TYMC).....	126
4.1.1.1 <i>Staphylococcus aureus</i>	126
4.1.1.2 <i>Pseudomonas aeruginosa</i>	127
4.1.2 Objectives of the Chapter.....	128
4.2 Materials and Methods	129
4.2.1 Method validation and media suitability testing	129
4.2.2 Preparation of creams for microbial limit studies	130
4.2.2.1 Preparation of 1% w/w Carbopol [®] 940 stock solution.....	131
4.2.2.2 Preparation of betamethasone 17-valerate creams	131
4.2.3 Preparation of solution and culture media for microbial limit studies	131
4.2.3.1 Preparation of buffered sodium chloride-peptone solution .	132
4.2.3.2 Preparation of required culture media	133
4.2.4 Sample Preparation	133
4.2.5 Performing microbial limit tests including method validation and media suitability testing	135
4.2.5.1 Total Aerobic Microbial Count (TAMC)	135
4.2.5.2 Total Combined Yeasts and Moulds Count (TYMC)	136
4.2.5.3 Tests for absence of specific microorganisms.....	137
4.2.5.3.1 Tests for absence of <i>Pseudomonas aeruginosa</i>	138
4.2.5.3.2 Tests for absence of <i>Staphylococcus aureus</i>	140
4.3 Results and Discussion	141
4.4 Conclusion	145

CHAPTER FIVE: STABILITY STUDIES OF BETAMETHASONE 17-VALERATE CREAMS PREPARED FROM PALM-OLEIN-IN-WATER EMULSIONS..... 146

5.1 Introduction.....	146
5.1.1 Types of stability studies.....	149
5.1.1.1 Real-time stability testing.....	150
5.1.1.2 Accelerated stability testing	151
5.1.1.3 Retained sample stability testing	152
5.1.1.4 Cyclic temperature stress testing	152
5.1.2 Objectives of the Chapter.....	153
5.2 Materials and Methods	153

5.2.1 Formulation of betamethasone 17-valerate creams for stability studies.....	153
5.2.1.1 Preparation of 1% (w/w) Carbopol [®] 940 stock solution.....	153
5.2.1.2 Preparation of betamethasone 17-valerate slurry	153
5.2.1.3 Preparation of 20% (w/w) palm-olein-in-water emulsions .	153
5.2.1.4 Preparation of betamethasone 17-valerate creams	154
5.2.2 Choice of container and closure.....	154
5.2.3 Performing stability studies	156
5.2.3.1 Characterization.....	156
5.2.3.1.1 Phase separation.....	156
5.2.3.1.2 Microscopical examination.....	156
5.2.3.1.3 Determination of oil droplet size	157
5.2.3.1.4 Performing pH measurement	157
5.2.3.1.5 Rheological measurements	157
5.2.4 Drug content analysis by HPLC.....	157
5.2.4.1 Apparatus.....	157
5.2.4.2 Materials	157
5.2.4.3 Chromatographic conditions	158
5.2.5 Photostability test.....	158
5.2.5.1 Irradiation of Betamethasone 17-valerate solution.....	158
5.2.6 Preparation of calibration standard solutions.....	159
5.2.6.1 Preparation of internal standard solution.....	159
5.2.6.2 Preparation of external standard solution	159
5.2.7 Sample Preparation for Drug Content.....	160
5.2.8 Calculation of drug concentration and shelf-life.....	160
5.3 Results and Discussion	162
5.3.1 Characterization	162
5.3.1.1 Phase separation	163
5.3.1.2 Rheological properties.....	166
5.3.1.2.1 Viscoelastic properties of the creams.....	167
5.3.2 Photodegradation of betamethasone 17-valerate	172
5.3.3 Degradation of betamethasone 17-valerate	175
5.4 Conclusion	185

CHAPTER SIX: GENERAL DISCUSSION..... 186

BIBLIOGRAPHY 197

APPENDIX A: List of Attended Conferences and Publications..... 219

APPENDIX B: Results from Instruments..... 221

LIST OF TABLES

<u>Table No.</u>		<u>Page No.</u>
2.1	Characteristics of palm oil and palm olein	12
2.2	Commonly used preservatives in pharmaceutical preparations	17
2.3	Compositions of the control and test emulsions	29
2.4	Solubility of betamethasone 17-valerate in various solvents. The data are presented as mean \pm SD, (n= 3)	38
2.5	Particle size and polydispersity index of control emulsions (C 1, C 2 and C 3) and betamethasone 17-valerate emulsions (T 1, T 2 and T 3) prepared from palm olein emulsions consisting of different concentration of Carbopol [®] 940. The formulations are stabilized with Span [®] 20/Tween [®] 20 (values are mean \pm SD, n=3)	42
2.6	Particle size and polydispersity index of control emulsions (C 1, C 2 and C 3) and betamethasone 17-valerate emulsions (T 1, T 2 and T 3) prepared from palm olein emulsions consisting of different concentration of Carbopol [®] 940 after six months. The formulations are stabilized with Span [®] 20/Tween [®] 20 (values are mean \pm SD, n=3)	43
2.7	Characteristics of emulsions produced from palm-olein-in-water emulsions and commercial products (values are mean \pm SD, n=3)	57
2.8	Zeta potential values and pH of freshly prepared betamethasone 17-valerate creams and control (values are mean \pm SD, n=3)	64
2.9	Data for skin hydration and moisturization properties by commercial topical products (R 1, R 2 and R 3) and test emulsions (T 1, T 2 and T 3) (values are mean \pm SD, n= 3)	66
3.1	Human and Animal Skin thickness Measurements	76
3.2	Some types of cytochrome P-450 enzyme isomers and their functions in mammalian cells	83
3.3	The ingredients used	97

3.4	Compositions of chemicals for PBS solution	98
3.5	Results of calibration standard solutions	109
3.6	The permeation parameters of test and reference samples	111
3.7	The percentage and amount of drug retained in all skin samples (values are mean \pm SD, n=3)	118
4.1	Compositions of chemicals included in buffered sodium chloride preparation	132
4.2	Compositions and uses of required culture media	133
4.3	Preparations of stock sample solutions	134
5.1	Stability criteria as required by the USP NF (2005)	146
5.2	Codes and titles of ICH guidelines	148
5.3	Climatic zones categorized by ICH guidelines	149
5.4	General storage conditions and duration of stability testing recommended by ICH guidelines	149
5.5	Storage conditions and duration of stability testing according to climatic zones and intended storage temperatures recommended by ICH guidelines for real-time stability testing	150
5.6	Sampling plan for stability studies	155
5.7	Oil droplet size and pH of palm olein-based cream containing 0.1% (w/w) betamethasone 17-valerate and stabilized with 0.3% (w/w) of Carbopol [®] 940(values are mean \pm SD, n= 3)	163
5.8	Degradation of betamethasone 17-valerate (values are mean \pm SD, n= 3)	172
5.9	Results of calibration standard solutions	175
5.10	Degradation of betamethasone 17-valerate creams prepared from 20% (w/w) palm olein emulsions containing 0.3% (w/w) Carbopol [®] 940 and stored inside plastic containers	179
5.11	Degradation of betamethasone 17-valerate creams prepared from 20% (w/w) palm olein emulsions containing 0.3% (w/w) Carbopol [®] 940 and stored inside aluminum collapsible tubes	180

5.12	Parameters for calculation of shelf-life of betamethasone 17-valerate creams packed inside plastic containers	184
5.13	Parameters for calculation of shelf-life of betamethasone 17-valerate creams packed inside aluminum tubes	184

LIST OF FIGURES

<u>Figure No.</u>		<u>Page No.</u>
1.1	The structures of human skin showing layers of skin with: (a) epidermal appendages, and (b) epidermal sub-layers	2
1.2	The layers of epidermis	3
1.3	Schematic diagram representing the “brick and mortar” model	4
1.4	The route of penetration of exogenous compounds into the skin via: 1.sweat pore; 2. stratum corneum and 3. hair follicles	5
2.1	Structures of (a) Span [®] 20 and (b) Tween [®] 20	14
2.2	Representative structures of Carbopol [®] 940 in acid (top) and neutral pH (bottom)	15
2.3	Chemical structure of methyl paraben sodium	19
2.4	Structure of propyl paraben sodium	19
2.5	Structure of chlorocresol	20
2.6	Structure of propylene glycol	21
2.7	Structural formula of betamethasone 17-valerate	22
2.8	Schematic diagram for preparation of betamethasone 17-valerate formulations from palm-olein-in-water emulsions	28
2.9	DSC thermogram of betamethasone 17-valerate	36
2.10	Calibration curves of betamethasone 17-valerate in: (a) methanol, (b) receptor medium and (c) distilled water: methanol 70: 30 (v/v)	37-38
2.11	Phase separation: (a) after 1 day, 1 month, 6 months and 12 months and (b) after 12 months of betamethasone 17-valerate and control formulations containing 20% palm olein emulsions, stabilised by Span [®] 20/Tween [®] 20 and thickened with 0.1% (C 1, T 1), 0.2% (C 2, T 2 and 0.3% (C 3, T 3) (w/w) of Carbopol [®] 940	40
2.12	Oil droplet size as a function of storage period of betamethasone 17-valerate emulsions and control emulsions	

	containing: (a) 0.1% (w/w) Carbopol [®] 940, (b) 0.2% (w/w) Carbopol [®] 940 and (c) 0.3% (w/w) Carbopol [®] 940 (values are mean \pm SD, n=3)	44-45
2.13	Effect of Carbopol [®] 940 concentration on size: (a) D(v, 90) and (b) D(v, 50) of both control emulsions without betamethasone 17-valerate and test emulsions over 12-month period (values are mean \pm SD, n=3)	45-46
2.14	Droplet size of freshly prepared betamethasone 17-valerate emulsions with: (a) 0.1% (w/w) Carbopol [®] 940, (b) 0.2% (w/w) Carbopol [®] 940, (c) 0.3% (w/w) Carbopol [®] 940 and same emulsions after 6 months with (d) 0.1% (w/w) Carbopol [®] 940, (e) 0.2% (w/w) Carbopol [®] 940 and (f) 0.3% (w/w) Carbopol [®] 940 when examined under optical microscope (40x)	50
2.15	Viscosity of control emulsion and betamethasone 17-valerate emulsion prepared from 20% (w/w) palm olein emulsions with 0.1% (w/w) of Carbopol [®] 940 as a function of shear rate	51
2.16	Viscosity of commercial creams (R 1, R 2 and R 3) and test emulsions (T 1, T 2 and T 3) containing 20% (w/w) palm olein with varied Carbopol [®] 940 concentrations as a function of shear rate	52
2.17	The effect of Carbopol [®] 940 concentration on yield stress of control emulsions without betamethasone 17-valerate and test emulsions	53
2.18	Flow curves (✕) and viscosity curves (✕) of control and test emulsions after 6 months containing 0.1% (w/w) Carbopol [®] 940: (a) C 1 and (b) T 1, 0.2% (w/w) Carbopol [®] 940: (c) C 2 and (d) T 2 and 0.3% (w/w) Carbopol [®] 940: (e) C 3 and (f) T 3	55-56
2.19	Storage modulus (G'), loss modulus (G'') and tan δ of betamethasone 17-valerate emulsions and control with: (a) 0.1% (w/w) Carbopol [®] 940, (b) 0.2% (w/w) Carbopol [®] 940 and (c) 0.3% (w/w) Carbopol [®] 940 as a function of oscillation shear stress	58-59
2.20	Storage modulus (G'), loss modulus (G'') and tan δ of betamethasone 17-valerate emulsions and control with: (a) 0.1% (w/w) Carbopol [®] 940, (b) 0.2% (w/w) Carbopol [®] 940 and (c) 0.3% (w/w) Carbopol [®] 940 as a function of frequency	60-61

2.21	Complex modulus (G^*) of Axcel betamethasone cream (R 1), Betasone cream (R 2), Betnovate cream (R 3) and betamethasone 17-valerate emulsions prepared from palm olein emulsions with 0.1% (T 1), 0.2% (T 2) and 0.3% (T 3) of Carbopol [®] 940 as a function of frequency (f)	63
3.1	Two types of diffusion cell systems: (a) Franz's static diffusion cell system and (b) Bronaugh's flow-through diffusion cell system	71
3.2	Schematic diagram showing possible pathways of drug diffusion across stratum corneum	80
3.3	Cutaneous metabolism of xenobiotics (X) by cytochrome P-450 enzyme (P450).	82
3.4	Cellulose ring structures showing (a) chain form and (b) boat form	87
3.5	Cross section of different membranes of different tortuosity (τ)	90
3.6	The schematic diagram of the transport of solute across a (a) porous and (b) non-porous membrane	92
3.7	(a) Commercial products and (b) Both commercial products and test emulsions	97
3.8	The experimental design of drug release rate comparison study	102
3.9	Calibration curve of betamethasone 17-valerate	109
3.10	HPLC Chromatogram of betamethasone 17-valerate (Conc. 1 $\mu\text{g/mL}$)	110
3.11	The permeation profiles of betamethasone 17-valerate from test (T1, T2, T3) and commercial samples (R1, R2, R3) through cellulose acetate membrane: values are mean \pm SD, n=3	111
3.12	HPLC chromatogram of blank skin sample	115
3.13	HPLC chromatogram of betamethasone 17-valerate (BV17), first degradant (FD) and second degradant (SD) retained in the rat skin after 6 hours	115
3.14	Amount of betamethasone 17-valerate retained in all skin samples after 6 hours (values are mean \pm SD, n=3)	118

4.1	Schematic diagram showing the steps of TAMC test	136
4.2	Schematic diagram showing the steps of TYMC test	137
4.3	Schematic diagram showing the experimental steps of test for absence of <i>Pseudomonas aeruginosa</i>	139
4.4	Schematic diagram showing the experimental steps of test for absence of <i>Staphylococcus aureus</i>	140
4.5	Results of TAMC Test showing that all control and test plates in both Set A and B were negative with no growth of microorganisms when non-sterile 20% (w/w) palm olein-based betamethasone 17-valerate creams thickened with 0.3% (w/w) of Carbopol® 940 were incubated with sterile casein soya bean digest agar media (SCD agar) at 30°C ± 0.5 for 5 days	142
4.6	Results of TYMC Test showing that all control and test plates in both Set A and B were negative with no growth of microorganisms when non-sterile 20% (w/w) palm olein-based betamethasone 17-valerate creams thickened with 0.3% (w/w) of Carbopol® 940 were incubated with sterile sabouraud-dextrose agar media (SDA agar) at 20°C ± 0.5 for 7 days	142
4.7	Results of Specific Microorganisms Test (<i>Pseudomonas aeruginosa</i>) showing the absence of microbial growth in all broth bottles of Set A and B when non-sterile 20% (w/w) palm olein-based betamethasone 17-valerate creams thickened with 0.3% (w/w) of Carbopol® 940 were incubated with sterile casein soya bean digest broth at 30°C ± 0.5 for 2 days	143
4.8	Results of <i>Pseudomonas aeruginosa</i> Test showing the absence of microbial growth in all control and test plates of both Set A and B when non-sterile 20% (w/w) palm olein-based betamethasone 17-valerate creams thickened with 0.3% (w/w) of Carbopol® 940 were sub-cultured and incubated with sterile cetrimide agar at 30°C ± 0.5 for 5 days	143
4.9	Results of Specific Microorganisms Test (<i>Staphylococcus aureus</i>) showing the absence of microbial growth in all broth bottles of Set A and B when non-sterile 20% (w/w) palm olein-based betamethasone 17-valerate creams thickened with 0.3% (w/w) of Carbopol® 940 were incubated with sterile casein soya bean digest broth at 30°C ± 0.5 for 2 days	144

4.10	Results of <i>Staphylococcus aureus</i> Test showing the absence of microbial growth in all control and test plates of both Set A and B when non-sterile 20% (w/w) palm olein-based betamethasone 17-valerate creams thickened with 0.3% (w/w) of Carbopol® 940 were sub-cultured and incubated with sterile molten Baird-Paker agar at 30°C ± 0.5 for 5 days	144
5.1	Grouping of samples for stability studies as mentioned in Table 5.6	155
5.2	Samples: (a) Group A stored at 4°C, (b) Group B stored at 25°C, (c) Group C stored at 40°C comparing to control sample and (d) all groups of samples after 3-month storage	164
5.3	Droplet size of betamethasone 17-valerate creams stabilized with 0.3% (w/w) Carbopol® 940 stored at: (a) control, (b) 25°C, (c) 40°C and (d) 4°C when examined under optical microscope (40 X) after 3 months	165
5.4	Comparison of flow curves and viscosity curves of freshly prepared control cream kept at normal laboratory conditions and test samples stored at: (a) 25°C, (b) 40°C and (c) 4°C for 3 months	166
5.5	Comparison of storage modulus (G'), loss modulus (G'') and tan δ of freshly prepared control cream kept at normal laboratory conditions and test samples stored at: (a) 25°C, (b) 40°C and (c) 4°C for 3 months as a function of oscillation shear stress	168-169
5.6	Comparison of storage modulus (G'), loss modulus (G'') and tan δ of freshly prepared control cream kept at normal laboratory conditions and test samples stored at: (a) 25°C, (b) 40°C and (c) 4°C for 3 months as a function of frequency	170-171
5.7	Chromatograms showing photodegradation of betamethasone 17-valerate (BV17) irradiated under fluorescent lamp for (a) 0.5, (b) 1, (c) 2, (d) 3, (e) 4, (f) 5, (g) 6 and (h) 7 hours with its degradation products, first degradant (FD) and second degradant (SD)	173
5.8	Schematic diagram of degradation of betamethasone 17-valerate into betamethasone 21-valerate and betamethasone	174
5.9	Calibration standard curve of betamethasone 17-valerate for stability studies	176
5.10	Chromatogram of betamethasone 17-valerate standard solution with norethisterone at a concentration of 25 µg/mL	176

5.11	Chromatograms of (a) blank cream containing 20% (w/w) palm olein and 0.3% (w/w) Carbopol [®] 940 stabilized with Span [®] 20/Tween [®] 20 and (b) test cream after 3 months storage at 25°C	177-178
5.12	First order degradation kinetics of betamethasone 17-valerate in palm olein-based creams stored in (a) plastic containers and (b) aluminum tubes at different temperatures	182-183
6.1	Proposed container and closure systems for palm olein-based betamethasone 17-valerate lotions	188
6.2	Betamethasone 17-valerate creams and lotions produced from 20% (w/w) palm olein-in-water emulsions (Palmisone [™] creams and lotions)	195

LIST OF EQUATIONS

<u>Equation No.</u>		<u>Page No.</u>
2.1	HLB mixture = $\sum_i^n X_i \text{HLB}_i$	14
2.2	Polydispersity = $\frac{\{D(v,90) - D(v,10)\}}{D(v,50)}$	30
2.3	$\sqrt{\tau} = \sqrt{\tau^o} + \sqrt{\eta\dot{\gamma}}$	32
3.1	$J = DC_0P/H$	81
3.2	$J = \frac{Dv \cdot K' \cdot \epsilon \cdot Cv}{h \cdot \tau}$	92
3.3	$Q = \left\{ C_n V + \sum_{i=1}^{n-1} (C_i S) \right\} / A$	107
3.4	$ER_{\text{flux}} = J_{\text{ss}}$ of test creams / J_{ss} of commercial creams	107
3.5	$K_p = J_{\text{ss}} / C_o$	108
3.6	Total amount of drug retained = drug concentration ($\mu\text{g/mL}$) x dilution factor (10mL)	108
4.1	1:10 dilution x aliquot plated x DF = result per milliliter	134
5.1	$\text{Log } K = \frac{-E_a}{RT} + \text{Log } A$	151
5.2	$\frac{A_x}{x} = F \left(\frac{A_s}{s} \right)$	161
5.3	Drug content (mg) = $\frac{\text{Drug concentration } (\mu\text{g/mL}) \times \text{Dilution factor (mL)}}{1000}$	161
5.4	% of drug remained = $\left(\frac{\text{Drug content in each month}}{\text{Initial drug content}} \right) 100$	161
5.5	Shelf life ($t_{0.9}$) = $\frac{0.1052}{K_{25}}$	162
5.6	Slope = $\frac{-K}{2.303}$	183

LIST OF SYMBOLS

τ	Shear stress
η	Viscosity
δ	Phase angle
ε	Membrane porosity
G^*	Complex modulus
G'	Storage modulus
G''	Loss modulus
$-E_a$	Activation energy
τ	Membrane tortuosity
mV	Millivolt
μS	MicroSiemens
Q	Cumulative amount of the compound released per surface area of the membrane
J_{ss}	Permeation rate at steady state
f	Frequency
$\dot{\gamma}$	Shear rate
τ°	Yield stress

LIST OF ABBREVIATIONS

API	Active pharmaceutical ingredient
B	Betamethasone
BP	British Pharmacopoeia
BSA	Bovine serum albumin
BV17	Betamethasone 17-valerate
BV21	Betamethasone 21-valerate
cGMP	Current good manufacturing practice
D(v, 10)	Diameter below which 10% of the particle size of the sample exists
D(v, 50)	Diameter below which 50% of the particle size of the sample exists or median volume
D(v, 90)	Diameter below which 90% of the particle size of the sample exists
DLVO theory	Deryaguin, Landau, Verwey and Overbeek theory
EP	European Pharmacopoeia
FDA	Food and Drug Administration
HLB	Hydrophile-lipophile balance
HPLC	High performance liquid chromatography
ICH guidelines	International Conference on Harmonisation Guidelines
ISO	International Organization for Standardization
JP	Japan Pharmacopoeia
LSE	Living skin equivalent
LVR	Linear viscoelastic region
OECD guidelines	Organisation for Economic Co-Operation and Development Guidelines
PBS	Phosphate buffer solution