List of Tables

Table 1.1.	Tabulated compilation of all therapy, drug examples, and their target	9
Table 1.2.	Summary of Apremilast pharmacokinetic parameters after 30 mg twice daily in psoriasis and psoriatic arthritis	14
Table 1.3.	Various nanocarriers used for topical delivery therapeutics used in psoriasis	18
Table 2.1.	Table representing linearity curve data	39
Table 2.2.	Accuracy and precision data of intraday and interday analysis of quality control samples	39
Table 2.3.	Forced degradation study representing impurity peaks retention time and percent degradation	45
Table 3.1.	Solubility of the drug in the lipid by physical observation technique	64
Table 3.2.	The quality target product profile of Apremilast loaded SLNs	65
Table 3.3.	Critical quality attributes for Apremilast loaded SLNs embedded gel	66
Table 3.4.	Risk Estimation Matrix (REM) for initial risk assessment of different material attributes and process parameters by qualitative analysis.	66
Table 3.5.	Failure Mode Evaluation and Analysis (FMEA) rank-order score based on the effects of material attributes and process parameters.	68
Table 3.6.	Experiment trials executed using Box-Behnken design and the obtained results	69
Table 3.7.	ANOVA for response particle Size and entrapment efficiency.	71
Table 3.8.	Constraint criteria for achievement of desired response variable and deviation (%) calculation of SLNs formulation.	73
Table 3.9.	Release kinetic mechanism data of Apremilast loaded SLNs dispersion	81
Table 3.10.	Summary of dermatokinetic evaluation of Apremilast loaded SLNs gel and free drug-loaded gel	92
Table 3.11.	Amount of Apremilast retained in the skin layers	94
Table 3.12.	Stability data of Apremilast loaded SLNs gel	95
Table 4.1.	The solubility of Apremilast in Liquid lipids	108
Table 4.2.	The design of experiments executed for optimization of NLCs dispersion.	110
Table 4.3.	ANOVA for response Particle Size and Entrapment efficiency	113
Table 4.4.	Constraint criteria for achievement of desired response variable and deviation (%) validation batch of NLCs dispersion.	114

Table 4.5.	Release kinetic mechanism data of Apremilast loaded NLCs dispersion.	119
Table 4.6.	Summary of dermatopharmacokinetic evaluation of Apremilast loaded NLCs gel and free drug-loaded gel	129
Table 4.7.	Amount of Apremilast retained in the skin layers	130
Table 4.8.	Stability data of Apremilast loaded NLCs gel	132
Table 5.1.	The QTPP parameters with respect to Apremilast loaded LCNPs	145
Table 5.2.	Critical quality attributes of Apremilast loaded LCNPs	145
Table 5.3.	Risk estimation matrix to determine the critical material attributes and process parameters.	147
Table 5.4.	The values of independent variables and response variables of Box Behnken trials.	148
Table 5.5.	ANOVA for response Particle Size and Entrapment efficiency.	151
Table 5.6.	Constraint criteria for achievement of desired response variable and deviation (%) obtained in validation batch of Apremilast loaded LCNPs dispersion.	153
Table 5.7.	The particle size and entrapment of 10 mL, 50 mL and 100 mL batches.	154
Table 5.8.	Release kinetic data of Apremilast loaded LCNPs dispersion.	159
Table 5.9.	Summary of dermatokinetic parameters of Apremilast LCNPs loaded gel and free drug-loaded gel	170
Table 5.10.	Amount of Apremilast retained in the skin layers	171
Table 5.11.	Stability data of Apremilast loaded LCNPs gel	172

List of Figures

Figure 1.1.	Anatomy of the skin.	2
Figure 1.2.	T-cell mediated pathogenesis mechanism in psoriasis	6
Figure 1.3.	Mechanism of phosphodiesterase-4 (PDE-4) inhibitor	11
Figure 1.4.	Nanocarriers permeation upon topical application	18
Figure 2.1.	Chromatographs obtained for Apremilast method validation	40
Figure 2.2.	Chromatographs obtained for force degradation study of Apremilast	43
Figure 2.3.	Chromatogram depicting the Apremilast in presence of skin tissue	46
Figure 3.1.	Ishikawa diagram depicting the potential CMAs and CPPs that affect the CQAs of Apremilast loaded SLNs formulation.	67
Figure 3.2A.	Box-Behnken optimization contour plot graph depicting effect of independent variables on particle size	72
Figure 3.2B.	Box-Behnken optimization 3D graph depicting effect of independent variables on particle size.	72
Figure 3.2C.	Box-Behnken optimization contour plot graph depicting the effect of independent variables on entrapment efficiency.	72
Figure 3.2D.	Box-Behnken optimization 3D graph depicting the effect of independent variables on entrapment efficiency.	72
Figure 3.3A.	The desirability contour plot for particle size of the batch with 100 mg lipid.	74
Figure 3.3B.	The desirability contour plot for entrapment efficiency of the batch with 100 mg lipid.	74
Figure 3.3C.	The desirability contour plot for particle size of the batch with 150 mg lipid.	75
Figure 3.3D.	The desirability contour plot for entrapment efficiency of the batch with 150 mg lipid.	75
Figure 3.4A.	ATR spectra of Apremilast pure drug.	76
Figure 3.4B.	ATR spectra of Apremilast loaded SLNs.	77
Figure 3.4C.	ATR spectra of Apremilast loaded SLNs excipients physical mixture.	77
Figure 3.5.	Apremilast loaded SLNs dispersion and particle size statistics graph.	78
Figure 3.6.	Apremilast loaded SLNs dispersion zeta potential graph.	79
Figure 3.7.	FESEM image of Apremilast loaded SLNs dispersion performed using Field Emission Scanning Electron Microscopy.	79

Figure 3.8.	The in-vitro drug release profile of Apremilast loaded SLNs dispersion (10 mL, 50 mL and 100 mL batch size) and free drug.	80
Figure 3.9.	Graphical representation of cell viability of Apremilast loaded SLNs dispersion and free drug.	81
Figure 3.10A.	The Fluorescence microscopic images of cell uptake data.	83
Figures 3.10B.	Cell uptake intensity of Coumarin-6 loaded SLNs and free Coumarin-6.	83
Figure 3.11.	The relative reduction of TNF- α mRNA in imiquimod induced psoriasis model.	84
Figure 3.12A.	Viscosity of Apremilast loaded SLNs gel formulation with respect to time.	85
Figure 3.12B.	Amplitude sweep test of Apremilast loaded SLNs gel formulation employing angular frequency.	85
Figure 3.12C.	Frequency sweep test of Apremilast loaded SLNs gel formulation (loss modulus and storage modulus).	86
Figure 3.12D.	Frequency sweep test of Apremilast loaded SLNs gel formulation (Complex viscosity).	86
Figure 3.13A.	Occlusive effect of Apremilast loaded SLNs gel and free drugloaded gel.	89
Figure 3.13B.	Ex-vivo skin permeation profiles of Apremilast loaded SLNs gel compared with free drug-loaded gel.	89
Figure 3.13C.	Skin retention study of Apremilast loaded SLNs gel compared with free drug-loaded gel	89
Figure 3.14.	In-vitro skin retention studies using Coumarin-6 loaded SLNs and free Coumarin-6.	91
Figure 3.15A.	Dermatokinetic profile of Apremilast loaded SLNs gel compared with free drug-loaded gel in the epidermis.	93
Figure 3.15B.	Dermatokinetic profile of Apremilast loaded SLNs gel compared with free drug-loaded gel in the dermis	93
Figure 3.16.	Skin retention of Apremilast in swiss albino mice treated with SLNs loaded gel, and free drug-loaded gel for 12 h and 24 h.	94
Figure 3.17.	The animal images for signs of irritation (inflammation and erythema) after and before application.	96
Figure 3.18.	The H&E staining histology data after 12 h and 24 h of application	97
Figure 4.1A.	Box-Behnken optimization contour plot graph depicting the effect of independent variables on particle size.	111
Figure 4.1B.	Box-Behnken optimization 3D graph depicting the effect of independent variables on particle size	111

Figure 4.1C.	Box-Behnken optimization contour plot graph depicting the effect of independent variables on entrapment efficiency.	112
Figure 4.1D.	Box-Behnken optimization 3D graph depicting the effect of independent variables on entrapment efficiency.	112
Figure 4.2.	The desirability contour plot for particle size and entrapment efficiency.	115
Figure 4.3.	The FTIR spectra of Apremilast, physical mixture, and Apremilast loaded NLCs.	116
Figure 4.4.	Apremilast loaded NLCs dispersion and particle size statistics graph.	118
Figure 4.5.	Apremilast loaded NLCs dispersion zeta potential graph.	118
Figure 4.6.	Morphology of Apremilast loaded NLCs dispersion performed using Field Emission Scanning Electron Microscopy.	118
Figure 4.7.	The in-vitro drug release profile of Apremilast loaded NLCs dispersion (10 mL, 50 mL and 100 mL) and free drug.	119
Figure 4.8.	Graphic representation of cell viability of Apremilast loaded NLCs dispersion and free drug.	120
Figure 4.9A.	The cell uptake Fluorescence microscopic images.	121
Figure 4.9B.	Cell uptake intensity of Coumarin-6 loaded NLCs and free Coumarin-6	121
Figure 4.10.	The relative reduction of TNF-α mRNA in the imiquimod induced psoriasis model	122
Figure 4.11A.	The viscosity of Apremilast loaded NLCs gel	123
Figure 4.11B.	Amplitude sweep test of Apremilast loaded NLCs gel	123
Figure 4.11C.	Frequency sweep test of Apremilast loaded NLCs gel (loss modulus and storage modulus).	124
Figure 4.11D.	Frequency sweep test of Apremilast loaded NLCs gel formulation (Complex viscosity).	124
Figure 4.12A.	Occlusive effect of Apremilast loaded NLCs gel and free drug-loaded gel	126
Figure 4.12B.	Ex-vivo skin permeation profiles of Apremilast loaded NLCs gel compared with free drug-loaded gel	126
Figure 4.12C.	Skin retention study of Apremilast loaded NLCs gel compared with free drug-loaded gel	126
Figure 4.13.	In-vitro skin retention studies using Coumarin-6 loaded NLCs and free Coumarin-6.	128
Figure 4.14A.	Dermatokinetic profile of Apremilast loaded NLCs gel compared with free drug-loaded gel in the epidermis	129
Figure 4.14B.	Dermatokinetic profile of Apremilast loaded NLCs gel compared with free drug-loaded gel in the dermis	130

Figure 4.15.	Skin retention of Apremilast in swiss albino mice treated with NLCs loaded gel, and free drug-loaded gel for 12 h and 24 h.	131
Figure 4.16.	The animal images for signs of irritation (inflammation and erythema) after and before application.	133
Figure 4.17.	The H&E staining histology data after 12 h and 24 h of application	134
Figure 5.1.	Ishikawa diagram depicting the potential CMAs and CPPs that affect the CQAs of Apremilast loaded LCNPs formulation.	146
Figure 5.2A.	The contour plot graph indicating the effect of independent variables on the particle size of Apremilast loaded LCNPs.	150
Figure 5.2B.	The 3D graph indicating the effect of independent variables on the particle size of Apremilast loaded LCNPs.	150
Figure 5.3A.	The contour plot graph indicating the effect of independent variables on the entrapment efficiency of Apremilast loaded LCNPs.	151
Figure 5.3B.	The 3D graph showing the effect of independent variables on the entrapment efficiency of Apremilast loaded LCNPs.	151
Figure 5.4.	The desirability contour plot, with maximum entrapment efficiency and minimum particle size.	152
Figure 5.5.	Apremilast loaded LCNPs dispersion and particle size statistics graph.	154
Figure 5.6.	Apremilast loaded LCNPs dispersion zeta potential graph.	154
Figure 5.7.	The morphology of the LCNPs formulation.	155
Figure 5.8.	The ATR spectra of the drug, physical mixture, and LCNPs formulation	156
Figure 5.9.	The powder X-Ray diffractogram of the Apremilast LCNPs formulation	157
Figure 5.10.	The polarized light microscopic images of the Apremilast loaded LCNPs dispersion (without and with cross polarizer)	158
Figure 5.11.	The in-vitro release profile of Apremilast loaded LCNPs dispersion.	159
Figure 5.12.	The MTT assay of Apremilast loaded LCNPs dispersion on HaCaT cell lines.	160
Figure 5.13A.	The cell uptake intensity of Coumarin-6 loaded LCNPs dispersion.	160
Figure 5.13B.	The cell uptake fluorescence images of Coumarin-6 loaded LCNPs dispersion.	160
Figure 5.14.	The relative reduction of TNF-α mRNA in the imiquimod induced psoriasis model	161
Figure 5.15A.	The viscosity of Apremilast loaded LCNPs gel	162
Figure 5.15B.	Amplitude sweep test of Apremilast loaded LCNPs gel	163

Figure 5.15C.	Frequency sweep test of Apremilast loaded LCNPs gel formulation (Complex viscosity).	163
Figure 5.15D.	Frequency sweep test of Apremilast loaded LCNPs gel (loss modulus and storage modulus).	164
Figure 5.16.	The in-vitro occlusive study of the Apremilast loaded LCNPs gel	164
Figure 5.17A.	Ex-vivo skin permeation profiles of Apremilast loaded LCNPs gel compared with free drug-loaded gel	165
Figure 5.17B.	Skin retention study of Apremilast loaded LCNPs gel compared with free drug-loaded gel	165
Figure 5.18.	In-vitro skin retention studies using Coumarin-6 loaded LCNPs dispersion and free Coumarin-6 dispersion	168
Figure 5.19A.	Dermatokinetic profile of Apremilast loaded LCNPs gel compared with free drug loaded gel in the epidermis	169
Figure 5.19B.	Dermatokinetic profile of Apremilast loaded LCNPs gel compared with free drug-loaded gel in the dermis	169
Figure 5.20.	Skin retention of Apremilast in swiss albino mice treated with LCNPs loaded gel, and free drug-loaded gel for 12 h and 24 h.	170
Figure 5.21.	The animal images for signs of irritation (inflammation and erythema) after and before application.	173
Figure 5.22.	The H&E staining histology data after 12 h and 24 h of application	174

List of abbreviations and symbols

% Percentage

μg Microgram

AUC Area under concentration

DLS Dynamic light scattering

SC Stratum corneum

KDa KiloDaltons

CD Cluster of differentiation

HLA Human leukocyte antigen

Th T-helper

TNF Tumor necrosis factor

IL Interleukin

CXCL chemokine ligand

NK Natural killer cells

JAK-STAT Janus kinase - Signal Transducers and Activators of Transcription

ACT1 Activator1

VEGF Vascular endothelial growth factor

IFN Interferon

NF-kB1 Nuclear factor signal pathway

PDE4 phosphodiesterase type 4

cAMP cyclic adenosine monophosphate

PKA protein kinase A

USFDA United States Food and Drug Administration

TYK2 tyrosine kinase2

PLGA Poly (D, L-lactide-coglycolide)

SLNs Solid lipid nanoparticles

NLCs Nanostructured lipid particles

LCNPs Lyotropic liquid crystalline nanoparticles

PASI Psoriatic Area Severity Index

cm Centimeter

mg milligram

g Gram

h Hour

min Minutes

g/mol Gram per mole

mL Milliliter

°C Degree Celsius

V_d Volume of distribution

C_{max} Maximum concentration

T_{max} Time taken to reach maximum concentration

 $t_{1/2}$ Half-life

CYP Cytochrome

L Liter

mV Milli volts

Nm Nanometer

TEWL Transepidermal water loss

The International Council for Harmonisation of Technical ICH

Requirements for Pharmaceuticals for Human Use

HPLC High-pressure liquid chromatography

μm Micrometer

mm Millimetre

cm Centimeter

μL Microliter

ng Nanogram

LOD Limit of detection

LOQ Limit of quantification

MQC Middle-quality control

M Molar

mM millimolar

μM micromolar

nM Nanomolar

 λ_{max} Lambda max

RSD Relative standard deviation

SD Standard deviation

mRNA Messenger Ribonucleic acid

miRNA Micro Ribonucleic acid

RHLB required hydrophilic-lipophilic balance

QbD Quality by design

QTPP Quality target product profile

CMA Critical material attributes

CPP Critical process parameters

CQA Critical quality attributes

FMEA Failure mode evaluation and analysis

RPN Risk Priority Number

BBD Box–Behnken design

RSM Response surface methodology

ATR-FTIR Attenuated total reflectance Fourier transform infrared

PDI Poly dispersibility index

FESEM Field Emission Scanning Electron Microscopy

rpm revolutions per minute

MTT 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyl tetrazolium bromide

HaCaT Cultured Human Keratinocyte

DMSO Dimethyl sulfoxide

DMEM Dulbecco's modified Eagle's medium

FBS Fetal bovine serum

DAPI 4',6-diamidino-2-phenylindole

FITC fluorescein isothiocyanate

CaCl₂ Calcium chloride

IC₅₀ inhibitory concentration

cDNA Complementary Deoxyribonucleic acid

RT-PCR Real time-quantitative polymerase chain reaction

GAPDH Glyceraldehyde 3-phosphate dehydrogenase

IMQ Imiquimod

s Seconds

Jss Steady-state flux

Kp permeability coefficient

K_e, Elimination rate constant

REM Risk Estimation Matrix

w/v Weight per volume

w/w Weight per weight

S/N Signal to noise

AIC Akaike Information Criteria

TLR Toll-like receptors

mPa.s millipascal-second

ANOVA Analysis of variance

DOE Design of experiments

< Less than

> More than

 \leq Less than equal to

 \geq More than equal to

= Equal to

 α Alpha

 $\beta \hspace{1cm} \text{Beta}$

 $\gamma \hspace{1cm} Gamma$