

List of Figures

Figure No.	Description	Page No.
2.1.	BCS Classification system.	13
2.2.	Distribution over the BCS classes of API's on the WHO's essential list of medicines (WHO LEM) from 2003 and of new chemical entities approved by the Food and Drug Administration (FDA appr. NCE's) from 2011 – 2013 [Müllers, 2015].	16
2.3.	Increasing order of challenge for oral formulation development.	17
2.4.	Solubility terms given by USP/NF.	18
2.5.	Classification of drug solubilities according to Ph. Eur. 7 th Edition.	18
2.6.	Formation of arterial plaque - cholesterol deposition and atherosclerosis.	20
2.7.	Schematic representation of supramolecular chemistry showing the phenomenon of selectivity.	29
2.8.	Classification of solid state forms.	32
2.9.	Classification of crystalline forms.	32
2.10.	Formation of a CoC.	34
2.11.	Schematic representation of polymorph, solvate or hydrate, CoC and salt [Kilinkissa, 2014].	35
2.12.	CD composition.	39
2.13.	Formation of binary CD inclusion complexes.	40
2.14.	Phase solubility behavior and profiles.	44
2.15.	Distinctive physicochemical properties of NCs [Salazar, 2013].	52
2.16.	Production of NCs.	54
2.17.	Eze structural formula.	61
2.18.	Structure of NA.	70
2.19.	Structure of ND.	72
2.20.	Structure of HPBCD.	74

2.21.	Structure of AA2G.	76
2.22.	Structure of TPGS.	77
2.23.	Structure of SLS.	80
5.1.	UV-VIS spectral scan of pure Eze in 0.01 N HCl (pH 2).	122
5.2.	UV-VIS standard calibration curve of pure Eze in 0.01 N HCl (pH 2).	122
5.3.	UV-VIS spectral scan of pure Eze in USP acetate buffer (pH 4.5).	123
5.4.	UV-VIS standard calibration curve of pure Eze in USP acetate buffer (pH 4.5).	123
5.5.	UV-VIS spectral scan of pure Eze in distilled water (measured pH 6.8).	124
5.6.	UV-VIS standard calibration curve of pure Eze in distilled water (measured pH 6.8).	124
5.7.	Phase solubility curves of liquid state CoC systems.	128
5.8.	Job's plots of liquid state CoC systems.	129
5.9.	UV-VIS spectral scan of pure NA in distilled water.	131
5.10.	UV-VIS standard calibration curve of pure NA in distilled water.	131
5.11.	UV-VIS spectral scan of pure ND in distilled water.	133
5.12.	UV-VIS standard calibration curve of pure ND in distilled water.	133
5.13.	FTIR spectra of CoCs.	138
5.14.	DSC thermograms of CoCs.	141
5.15.	X-ray diffractograms of CoCs.	143
5.16.	SEM photomicrographs of (A) Eze; (B) NA; (C) ND; (D) Eze-NA; (E) Eze-ND.	144
5.17.	TGA graphs of CoCs.	145
5.18.	Dissolution profiles of pure drug, PMs, Eze-NA, and Eze-ND (vertical bars represent SD, n = 6).	149
5.19.	Dissolution profiles of Eze-NA and Eze-ND from stability studies (vertical bars represent SD, n = 6).	151
5.20.	HPLC chromatograms of pure Eze (analytical) sample, blank plasma and plasma spiked Eze (bioanalytical) sample.	155
5.21.	HPLC-UV standard calibration curve of pure Eze analytical samples.	156

5.22.	HPLC-UV standard calibration curve of plasma spiked Eze bioanalytical samples.	156
5.23.	Pharmacokinetic profiles of pure Eze and optimized CoCs (vertical bars represent SD, n = 6). Inset shows the profile up to 4 h.	161
5.24.	Percent reduction in the total cholesterol levels achieved by pure Eze and CoC formulations (vertical bars represent SD, n = 6).	167
5.25.	Schematic diagram showing formation of Eze-NA.	171
5.26.	Schematic diagram showing formation of Eze-ND.	171
5.27.	Gist of effect of cocrystallization formulation approach on Eze performance.	172
6.1.	Structure of ezetimibe showing proton assignments.	175
6.2.	Eze solubility diagram in a fixed concentration of HPBCD (2% w/v) with increasing concentrations of TPGS.	188
6.3.	Eze solubility diagram in a fixed concentration of HPBCD (2% w/v) with increasing concentrations of AA2G.	189
6.4.	Phase solubility curves of liquid state binary and ternary systems.	190
6.5.	Job's plots of liquid state binary and ternary systems.	192
6.6.	Benesi–Hildebrand plots - Double reciprocal plots of binary and ternary systems.	194
6.7.	Benesi–Hildebrand plots - Reciprocal plots of binary and ternary systems.	195
6.8.	FTIR spectra of parent compounds, physical mixture and complexes.	198
6.9.	DSC thermograms of parent compounds, physical mixture and complexes.	200
6.10.	X-ray diffractograms of parent compounds, physical mixture and complexes.	202
6.11.	SEM photomicrographs of A:Eze; B:HPBCD; C:AA2G; D:E-CD; E:E-CD-AA2G; F:E-CD-TPGS.	204
6.12.	NMR spectra of pure Eze and complexes.	205
6.13.	Dissolution profiles of pure drug, binary and ternary complexes (vertical bars represent SD, n = 6).	216
6.14.	Dissolution profiles of ternary complexes before and after stability study (vertical bars represent SD, n = 6).	219

6.15.	Pharmacokinetic profiles of pure Eze and optimized ternary complexes (vertical bars represent SD, n = 6). Inset shows the profile up to 4 h.	222
6.16.	Percent reduction in the total cholesterol levels achieved by CD formulations (vertical bars represent SD, n = 6).	225
6.17.	Schematic diagram showing formation of binary and ternary CD complexes of Eze.	228
6.18.	Gist of effect of ternary CD complexation formulation approach on Eze performance.	229
7.1.	Pareto analysis of effect of independent variables applied using PBD on the response, PS.	259
7.2.	'One factor at a time' analysis of effect of independent variables on the response, PS.	262
7.3.	Pareto analysis of effect of independent variables applied using PBD on the response, PDI.	263
7.4.	'One factor at a time' analysis of effect of independent variables on the response, PDI.	266
7.5.	Pareto analysis of effect of independent variables applied using PBD on the response, ZP.	267
7.6.	'One factor at a time' analysis of effect of independent variables on the response, ZP.	270
7.7.	A. Contour plots and B. Response surface plots - showing effect of any two independent variables applied using BBD on the response, PS.	277
7.8.	A. Contour plots and B. Response surface plots - showing effect of any two independent variables applied using BBD on the response, PDI.	282
7.9.	A. Contour plots and B. Response surface plots - showing effect of any two independent variables applied using BBD on the response, ZP.	287
7.10.	A. Contour plots and B. Response surface plots - showing effect of any two independent variables applied using CCD on the response, PS.	295
7.11.	A. Contour plots and B. Response surface plots - showing effect of any two independent variables applied using CCD on the response, PDI.	300
7.12.	A. Contour plots and B. Response surface plots - showing effect of any two independent variables applied using CCD on the response, ZP.	305

7.13.	Particle size distribution graph of F3.	312
7.14.	Particle size distribution graph of F8.	312
7.15.	Zeta potential – mobility distribution graph of F3.	313
7.16.	Zeta potential – mobility distribution graph of F8.	314
7.17.	FTIR spectra of pure drug, excipients, PMs and NCs.	316
7.18.	DSC thermograms of pure drug, excipients, PMs and NCs.	317
7.19.	X-ray diffractograms of pure drug, excipients, PMs and NCs.	318
7.20.	SEM images. A: Pure Eze at 2000X. B: F8 at 500X C: F8 at 2000X D: AA2G at 2000X. E: F3 at 500X. F: F3 at 2000X.	320
7.21.	AFM picture of plain drug.	321
7.22.	AFM picture of F8.	322
7.23.	Dissolution profiles of pure drug, PMs and optimized NC formulations (vertical bars represent SD, n = 6).	325
7.24.	Dissolution profiles of stability batches against fresh batches of NCs (vertical bars represent SD, n = 6).	330
7.25.	Pharmacokinetic profiles of pure drug suspension and optimized NCs (vertical bars represent SD, n = 6). Inset shows the profile up to 4 h.	333
7.26.	Antihypercholesterolemic activity of pure drug suspension, control, and optimized NCs (vertical bars represent SD, n = 6).	336
7.27.	Pharmacodynamic performances of pure drug suspension, control, F3 and F8 (vertical bars represent SD, n = 6).	338
7.28.	Schematic diagram showing formation of ANCs of Eze.	341
7.29.	Schematic diagram showing formation of TNCs of Eze.	342
7.30.	Gist of effect of nanocrystallization formulation approach on Eze performance.	343
8.1.	Solubility of pure Eze and optimized formulations in distilled water (vertical bars represent SD, n = 3).	358
8.2.	Dissolution parameter, $t_{80\%}$ of optimized formulations and Ezentia in USP acetate buffer media (pH 4.5) with 0.45% w/v SLS (vertical bars represent SD, n = 6).	359
8.3.	DE ₄₅ of pure Eze, optimized formulations and Ezentia, in USP acetate buffer media (pH 4.5) with 0.45% w/v SLS (vertical bars represent SD, n = 6).	360
8.4.	Dissolution profiles of pure drug, Ezentia and optimized formulations in 0.01 N HCl (pH 2) containing 0.45% w/v SLS	361

(vertical bars represent SD, n = 6).

8.5.	Dissolution profiles of pure drug, Ezentia and optimized formulations in USP acetate buffer (pH 4.5) containing 0.45% w/v SLS (vertical bars represent SD, n = 6).	362
8.6.	Dissolution profiles of pure drug, Ezentia and optimized formulations in distilled water (measured pH 6.8) containing 0.45% w/v SLS (vertical bars represent SD, n = 6).	363
8.7.	Dissolution parameters: $t_{80\%}$ of optimized formulations and Ezentia in A. 0.01N HCl (pH 2) with 0.45% w/v SLS and B. distilled water (pH 7.4) with 0.45% w/v SLS; DE_{45} of pure Eze, optimized formulations and Ezentia in C. 0.01N HCl (pH 2) with 0.45% w/v SLS and D. distilled water (pH 7.4) with 0.45% w/v SLS (vertical bars represent SD, n = 6).	365
8.8.	FTIR spectra, DSC thermograms and PXRD graphs of a stability study batch of Eze-ND against the respective fresh batch.	367
8.9.	FTIR spectra, DSC thermograms and PXRD graphs of a stability study batch of E-CD-TPGS against the respective fresh batch.	368
8.10.	FTIR spectra, DSC thermograms and PXRD graphs of a stability study batch of ESTNC –F8 against the respective fresh batch.	369
8.11.	Pharmacokinetic profiles of pure Eze, Ezentia, Ezentia suspension and optimized formulations (vertical bars represent SD, n = 6) up to 24 h.	373
8.12.	Pharmacokinetic profiles of pure Eze, Ezentia, Ezentia suspension and optimized formulations (vertical bars represent SD, n = 6) up to 4 h.	374
8.13.	Percent decrease in total plasma cholesterol levels achieved by various treatment groups.	379
8.14.	Percent decrease in plasma triglyceride levels achieved by various treatment groups.	379
8.15.	Percent increase in plasma HDL levels achieved by various treatment groups.	380
8.16.	Percent decrease in plasma LDL levels achieved by various treatment groups.	380
8.17.	Percent decrease in plasma VLDL levels achieved by various treatment groups.	381
8.18.	Percent decrease in Atherogenic Coefficient achieved by various treatment groups.	381
8.19.	Percent decrease in Atherogenic Index of Plasma achieved by various treatment groups.	382

8.20.	Percent decrease in CHOLINDEX achieved by various treatment groups.	382
8.21.	Percent decrease in Cardiac Risk Ratio or Castelli's Risk Index I achieved by various treatment groups.	383
8.22.	Percent decrease in Castelli's Risk Index II achieved by various treatment groups.	383
8.23.	Percent decrease in total plasma cholesterol levels – A. Before dose reduction (standard group and test groups received 1 mg/kg/day equivalent Eze) and B. After dose reduction (E-CD-TPGS and Eze-ND were dosed at 0.5 mg/kg/day equivalent Eze; ESTNC-F8 was dosed at 0.2 mg/kg/day equivalent Eze while plain Eze and Ezentia treatment groups received 1 mg/kg/day equivalent Eze).	395
8.24.	Percent decrease in plasma triglyceride levels – A. Before dose reduction (standard group and test groups received 1 mg/kg/day equivalent Eze) and B. After dose reduction (E-CD-TPGS and Eze-ND were dosed at 0.5 mg/kg/day equivalent Eze; ESTNC-F8 was dosed at 0.2 mg/kg/day equivalent Eze while plain Eze and Ezentia treatment groups received 1 mg/kg/day equivalent Eze).	396
8.25.	Percent increase in plasma HDL levels – A. Before dose reduction (standard group and test groups received 1 mg/kg/day equivalent Eze) and B. After dose reduction (E-CD-TPGS and Eze-ND were dosed at 0.5 mg/kg/day equivalent Eze; ESTNC-F8 was dosed at 0.2 mg/kg/day equivalent Eze while plain Eze and Ezentia treatment groups received 1 mg/kg/day equivalent Eze).	397
8.26.	Percent decrease in plasma LDL levels – A. Before dose reduction (standard group and test groups received 1 mg/kg/day equivalent Eze) and B. After dose reduction (E-CD-TPGS and Eze-ND were dosed at 0.5 mg/kg/day equivalent Eze; ESTNC-F8 was dosed at 0.2 mg/kg/day equivalent Eze while plain Eze and Ezentia treatment groups received 1 mg/kg/day equivalent Eze).	398
8.27.	Percent decrease in plasma VLDL levels – A. Before dose reduction (standard group and test groups received 1 mg/kg/day equivalent Eze) and B. After dose reduction (E-CD-TPGS and Eze-ND were dosed at 0.5 mg/kg/day equivalent Eze; ESTNC-F8 was dosed at 0.2 mg/kg/day equivalent Eze while plain Eze and Ezentia treatment groups received 1 mg/kg/day equivalent Eze).	399
8.28.	Percent decrease in Atherogenic Coefficient – A. Before dose	400

- reduction (standard group and test groups received 1 mg/kg/day equivalent Eze) and B. After dose reduction (E-CD-TPGS and Eze-ND were dosed at 0.5 mg/kg/day equivalent Eze; ESTNC-F8 was dosed at 0.2 mg/kg/day equivalent Eze while plain Eze and Ezentia treatment groups received 1 mg/kg/day equivalent Eze).
- 8.29. Percent decrease in Atherogenic Index of Plasma – A. Before dose reduction (standard group and test groups received 1 mg/kg/day equivalent Eze) and B. After dose reduction (E-CD-TPGS and Eze-ND were dosed at 0.5 mg/kg/day equivalent Eze; ESTNC-F8 was dosed at 0.2 mg/kg/day equivalent Eze while plain Eze and Ezentia treatment groups received 1 mg/kg/day equivalent Eze). 401
- 8.30. Percent decrease in CHOLINDEX – A. Before dose reduction (standard group and test groups received 1 mg/kg/day equivalent Eze) and B. After dose reduction (E-CD-TPGS and Eze-ND were dosed at 0.5 mg/kg/day equivalent Eze; ESTNC-F8 was dosed at 0.2 mg/kg/day equivalent Eze while plain Eze and Ezentia treatment groups received 1 mg/kg/day equivalent Eze). 402
- 8.31. Percent decrease in Cardiac Risk Ratio or Castelli’s Risk Index I – A. Before dose reduction (standard group and test groups received 1 mg/kg/day equivalent Eze) and B. After dose reduction (E-CD-TPGS and Eze-ND were dosed at 0.5 mg/kg/day equivalent Eze; ESTNC-F8 was dosed at 0.2 mg/kg/day equivalent Eze while plain Eze and Ezentia treatment groups received 1 mg/kg/day equivalent Eze). 403
- 8.32. Percent decrease in Castelli’s Risk Index II – A. Before dose reduction (standard group and test groups received 1 mg/kg/day equivalent Eze) and B. After dose reduction (E-CD-TPGS and Eze-ND were dosed at 0.5 mg/kg/day equivalent Eze; ESTNC-F8 was dosed at 0.2 mg/kg/day equivalent Eze while plain Eze and Ezentia treatment groups received 1 mg/kg/day equivalent Eze). 404