

LIST OF TABLES

Table No.	Table Title	Page No.
Table 1.1	Marketed pharmaceutical nanosuspension formulations manufactured by top down approaches.	6
Table 1.2	The fundamental properties of α -, β - and γ -CDs.	29
Table 1.3	Chemical structures of various cyclodextrin derivatives.	30
Table 1.4	Solubility and Pharmacopoeial monographs of CDs that are used as excipients in pharmaceutical formulations.	31
Table 3.1	Summary of calibration data for DAR in Methanol, Distilled Water, Phosphate Buffer pH 6.8, Acetate Buffer pH 4.5 and 0.1N HCl by UV spectroscopy.	70
Table 3.2	Summary of linearity parameters for DAR in Methanol, Distilled Water, Phosphate Buffer pH 6.8, Acetate Buffer pH 4.5 and 0.1N HCl by UV spectroscopy.	72
Table 3.3	Summary of intra-day precision and accuracy for DAR in Methanol, Distilled Water, Phosphate Buffer pH 6.8, Acetate Buffer pH 4.5 and 0.1N HCl by UV spectroscopy.	73
Table 3.4	Summary of inter-day precision and accuracy for DAR in Methanol, Distilled Water, Phosphate Buffer pH 6.8, Acetate Buffer pH 4.5 and 0.1N HCl by UV spectroscopy.	73
Table 3.5	Summary of LOD and LOQ values for DAR in Methanol, Distilled Water, Phosphate Buffer pH 6.8, Acetate Buffer pH 4.5 and 0.1N HCl by UV spectroscopy.	74
Table 3.6	System suitability parameters of RP-HPLC method for estimation of DAR in formulations.	78
Table 3.7	Calibration data of RP- HPLC method for estimation of DAR in formulations.	78
Table 3.8	Summarized linearity parameters of RP-HPLC method for estimation of DAR in formulations.	79
Table 3.9	Intra-day and inter-day precision of RP-HPLC method for estimation of DAR in formulations.	79
Table 3.10	Intra-day and inter-day accuracy of RP-HPLC method for estimation of DAR in formulations.	80
Table 3.11	LOD and LOQ of RP-HPLC method for estimation of DAR in formulations.	80
Table 3.12	Robustness and ruggedness of RP-HPLC method for the estimation of DAR in formulations.	80
Table 3.13	Stability of DAR solutions used in RP-HPLC method for estimation of drug in formulations.	81

Table 3.14	System suitability parameters of RP-HPLC method for estimation of DAR in HBSS buffer.	84
Table 3.15	Calibration data of RP-HPLC method for estimation of DAR in HBSS buffer.	85
Table 3.16	Summarized linearity parameters of RP-HPLC method for estimation of DAR in HBSS buffer.	85
Table 3.17	LOD and LOQ of RP-HPLC method for estimation of DAR in HBSS buffer.	85
Table 3.18	Intra-day and inter-day precision of RP-HPLC method for estimation of DAR in HBSS buffer.	86
Table 3.19	Intra-day and inter-day accuracy of RP-HPLC method for estimation of DAR in HBSS buffer.	86
Table 3.20	Stability of DAR solutions used in RP-HPLC method for estimation of drug in HBSS buffer.	87
Table 3.21	Physicochemical properties of rhein and FNB.	88
Table 3.22	System suitability parameters of RP-HPLC method for estimation of rhein in plasma.	92
Table 3.23	Calibration data of RP-HPLC method for estimation of rhein in plasma.	92
Table 3.24	Back calculation of extracted concentration of rhein in plasma by recorded peak area of calibration curve standards.	93
Table 3.25	Summarized linearity parameters of RP-HPLC method for estimation of rhein in plasma.	93
Table 3.26	Intra-day and inter-day precision of RP-HPLC method for estimation of rhein in plasma.	93
Table 3.27	Intra-day and inter-day accuracy of RP-HPLC method for estimation of rhein in plasma.	94
Table 3.28	Absolute recovery of rhein and FNB (ISTD) from plasma.	94
Table 3.29	Stability of rhein in plasma used in RP-HPLC method.	94
Table 3.30	Summary of calibration data for FBX in Methanol, Distilled Water, Phosphate Buffer pH 6.8, Acetate Buffer pH 4.5 and 0.1N HCl by UV spectroscopy.	100
Table 3.31	Summary of linearity parameters for FBX in Methanol, Distilled Water, Phosphate Buffer pH 6.8, Acetate Buffer pH 4.5 and 0.1N HCl by UV spectroscopy.	100
Table 3.32	Summary of LOD and LOQ values for FBX in Methanol, Distilled Water, Phosphate Buffer pH 6.8, Acetate Buffer pH 4.5 and 0.1N HCl by UV spectroscopy.	100
Table 3.33	Summary of intra-day precision and accuracy for FBX in Methanol, Distilled Water, Phosphate Buffer pH 6.8, Acetate Buffer pH 4.5 and 0.1N HCl by UV spectroscopy.	101

Table 3.34	Summary of inter-day precision and accuracy for FBX in Methanol, Distilled Water, Phosphate Buffer pH 6.8, Acetate Buffer pH 4.5 and 0.1N HCl by UV spectroscopy.	101
Table 3.35	System suitability parameters of RP-HPLC method for estimation of FBX in formulations.	104
Table 3.36	Calibration data of RP-HPLC method for estimation of FBX in formulations.	104
Table 3.37	Summarized linearity parameters of RP-HPLC method for estimation of FBX in formulation.	105
Table 3.38	Intra-day and inter-day precision of RP-HPLC method for estimation of FBX in formulations.	105
Table 3.39	Intra-day and inter-day accuracy of RP-HPLC method for estimation of FBX in formulation.	106
Table 3.40	LOD and LOQ of RP-HPLC method for estimation of FBX in formulation.	106
Table 3.41	Robustness and ruggedness of RP-HPLC method for estimation of FBX in formulation.	107
Table 3.42	Stability of FBX solutions used in RP-HPLC method for estimation of drug in formulations.	107
Table 3.43	System suitability parameters of RP-HPLC method for estimation of FBX in HBSS buffer.	109
Table 3.44	Calibration data of RP-HPLC method for estimation of FBX in HBSS buffer.	110
Table 3.45	Summarized linearity parameters of RP-HPLC method for estimation of FBX in HBSS buffer.	110
Table 3.46	Intra-day and inter-day precision of RP-HPLC method for estimation of FBX in HBSS buffer.	111
Table 3.47	Intra-day and inter-day accuracy of RP-HPLC method for estimation of FBX in HBSS buffer.	111
Table 3.48	LOD and LOQ of RP-HPLC method for estimation of FBX in HBSS buffer.	111
Table 3.49	Stability of FBX solutions used in RP-HPLC method for estimation of drug in HBSS buffer.	112
Table 3.50	Physicochemical properties of FBX and INDM.	113
Table 3.51	System suitability parameters of RP-HPLC method for estimation of FBX in plasma.	115
Table 3.52	Calibration data of RP-HPLC method for estimation of FBX in plasma.	116
Table 3.53	Back calculation of extracted concentration of FBX in plasma by recorded peak area of calibration curve standards.	116
Table 3.54	Summarized linearity parameters of RP-HPLC method for estimation of FBX in plasma.	116

Table 3.55	Intra-day and inter-day precision of RP-HPLC method for estimation of FBX in plasma.	117
Table 3.56	Intra-day and inter-day accuracy of RP-HPLC method for estimation of FBX in plasma.	117
Table 3.57	Absolute recovery of FBX and INDM (ISTD) from plasma.	118
Table 3.58	Stability of FBX in plasma used in RP-HPLC method.	118
Table 4.1	Relevant properties and chemical formula of excipients tried to prepare a stabilized Nanosuspension.	125
Table 4.2	Coded translation of formulation variables of 3 ³ full factorial design for DAR-NS.	126
Table 4.3	Layout of factor combinations for DAR-NS using 3 ³ full factorial designs (coded values).	127
Table 4.4	Effect of beads type on MPS and PDI of DAR-NS.	142
Table 4.5	Effect of ratio of beads on MPS and PDI of DAR-NS.	143
Table 4.6	Effect of volume of milling media on MPS and PDI of DAR-NS.	143
Table 4.7	Effect of type of stabilizer on MPS and PDI of DAR-NS.	144
Table 4.8	Combinations of independent variables (X ₁ , X ₂ and X ₃) and observed, predicted and residual values of responses Y ₁ and Y ₂ as per 3 ³ full factorial design for formulation of DAR-NS.	147
Table 4.9	Fit summary statistics of responses Y ₁ and Y ₂ as per 3 ³ full factorial design for formulation of DAR-NS.	148
Table 4.10	Results of model and coefficient estimation by ANOVA and Student's 't' test for responses Y ₁ (PS) and Y ₂ (SS) of DAR-NS.	149
Table 4.11	ANOVA of full and reduced models for PS and SS of DAR-NS.	150
Table 4.12	Check point analysis, Student's t-test and NE determination of PS and SS of DAR-NS.	157
Table 4.13	Effect of cryoprotectants and their concentration on PS of freeze dried DAR-NS after redispersion in distilled water.	159
Table 4.14	Statistical representation of % Cumulative drug release versus sampling time of DAR-P, DAR-M and freeze dried DAR-NS in phosphate buffer pH-6.8 (PB), acetate buffer pH-4.5 (AB), 0.1N HCl and water.	166
Table 4.15	Comparision of various dissolution parameters of DAR-P, DAR-M and freeze dried DAR-NS in phosphate buffer pH-6.8 (PB), acetate buffer pH-4.5 (AB), 0.1N HCl and water.	168
Table 4.16	Physical stability (i.e. PS, PDI and ZP) of DAR-NS at different time intervals stored at 5°C±3°C and room temperature.	168
Table 4.17	Chemical stability (i.e. percentage drug content) of DAR-NS at different time intervals stored. at 5°C±3°C and room temperature.	169
Table 4.18	In vitro cytotoxicity studies of DAR-P and DAR-NS in Caco2 cell lines at 4 hours, 24 hours and 48 hours.	170
Table 4.19	IC ₅₀ values of DAR-P and DAR-NS in Caco2 cell lines at 4	170

	hours, 24 hours and 48 hours.	
Table 4.20	Apparent permeability coefficient (P_{app}) from apical to basolateral for DAR-P, DAR-M and DAR-NS using Caco-2 cells model.	172
Table 4.21	Statistical representation of rhein plasma profile for DAR-P, DAR-M and DAR-NS in Albino rabbits following oral administration.	174
Table 4.22	Pharmacokinetic parameters after oral administration of DAR-P, DAR-M and DAR-NS in Albino rabbits.	175
Table 4.23	Comparison of slopes, intercepts, R^2 and K_s of phase solubility studies in water, phosphate buffer pH-6.8 and HCl pH-1.2 for DAR with CDs.	193
Table 4.24	Inclusion efficiency values of all Freeze dried inclusion complexes, kneaded mixtures and physical mixtures of DAR with cyclodextrins (β -CD, HP- β -CD, M- β -CD and γ -CD) in 1:1, 1:2 and 1:3 molar ratios of DAR:CD.	194
Table 4.25	Statistical representation of % Cumulative drug release versus sampling time of DAR-P, DAR-M and Freeze dried DAR-IC in phosphate buffer pH-6.8 (PB), acetate buffer pH-4.5 (AB), 0.1N HCl and water.	202
Table 4.26	Comparison of various dissolution parameters of DAR-P, DAR-M and Freeze dried DAR-IC in phosphate buffer pH-6.8 (PB), acetate buffer pH-4.5 (AB), 0.1N HCl and water.	202
Table 4.27	Chemical stability (i.e. percentage drug content) of Freeze dried DAR-IC at different time intervals stored at $5^\circ\text{C}\pm 3^\circ\text{C}$ and room temperature.	203
Table 4.28	In vitro cytotoxicity studies of DAR-P and freeze dried DAR-IC in Caco2 cell lines at 4 hours, 24 hours and 48 hours.	204
Table 4.29	IC_{50} values of DAR-P and freeze dried DAR-IC in Caco2 cell lines at 4 hours, 24 hours and 48 hours.	204
Table 4.30	Apparent permeability coefficient (P_{app}) from apical to basolateral for DAR-P, DAR-M and freeze dried DAR-IC using Caco-2 cells model.	206
Table 4.31	Statistical representation of rhein plasma profile for DAR-P, DAR-M and freeze dried DAR-IC in Albino rabbits following oral administration.	208
Table 4.32	Pharmacokinetic parameters after oral administration of DAR-P, DAR-M and freeze dried DAR-IC in Albino rabbits.	208
Table 5.1	Coded translation of formulation variables of 3^3 full factorial design for FNX-NS.	223
Table 5.2	Formulation of FBX-NS using 3^3 factorial designs (coded values).	223
Table 5.3	Effect of beads type on MPS and PDI of FBX-NS.	233

Table 5.4	Effect of ratio of beads on MPS and PDI of FBX-NS.	234
Table 5.5	Effect of volume of milling media on MPS and PDI of FBX-NS.	234
Table 5.6	Effect of type of stabilizer on MPS and PDI of FBX-NS.	235
Table 5.7	Combinations of independent variables (X_1 , X_2 and X_3) and observed, predicted and residual values of responses Y_1 and Y_2 as per 3^3 full factorial design for formulation of FBX-NS.	237
Table 5.8	Fit summary statistics of responses Y_1 and Y_2 as per 3^3 full factorial design for formulation of FBX-NS.	238
Table 5.9	Results of model and coefficient estimation by ANOVA and Student's 't' test for responses Y_1 (PS) and Y_2 (SS) of FBX-NS.	240
Table 5.10	Analysis of Variance (ANOVA) of full and reduced models for PS and SS of FBX-NS.	241
Table 5.11	Check point analysis, Student's t-test analysis and NE determination of PS and SS of FBX-NS.	247
Table 5.12	Effect of cryoprotectants and their concentration on PS of freeze dried FBX-NS after redispersion in distilled water.	249
Table 5.13	Statistical representation of % Cumulative drug release versus sampling time of FBX-P, FBX-M and freeze dried FBX-NS in phosphate buffer pH-6.8 (PB), acetate buffer pH-4.5 (AB), 0.1N HCl and water.	256
Table 5.14	Comparision of various dissolution parameters of FBX-P, FBX-M and freeze dried FBX-NS in phosphate buffer pH-6.8 (PB), acetate buffer pH-4.5 (AB), 0.1N HCl and water.	258
Table 5.15	Physical stability (i.e. PS, PDI and ZP) of FBX-NS at different time intervals stored at $5^{\circ}\text{C}\pm 3^{\circ}\text{C}$ and room temperature.	259
Table 5.16	Chemical stability (i.e. percentage drug content) of FBX-NS at different time intervals stored at $5^{\circ}\text{C}\pm 3^{\circ}\text{C}$ and room temperature.	259
Table 5.17	In vitro cytotoxicity studies of FBX-P and FBX-NS in Caco2 cell lines at 4 hours, 24 hours and 48 hours.	260
Table 5.18	IC_{50} values of FBX-P and FBX-NS in Caco2 cell lines at 4 hours, 24 hours and 48 hours.	262
Table 5.19	Apparent permeability coefficient (P_{app}) from apical to basolateral for FBX-P, FBX-M and FBX-NS using Caco-2 cells model.	263
Table 5.20	Statistical representation of FBX plasma profile for FBX-P, FBX-M and FBX-NS in Albino rabbits following oral administration.	265
Table 5.21	Pharmacokinetic parameters after oral administration of FBX-P, FBX-M and FBX-NS in Albino rabbits.	265
Table 5.22	Comparison of slopes, intercepts, R^2 and K_s of phase solubility studies in water, phosphate buffer pH-6.8 and HCl pH-1.2 for FBX with CDs.	276

Table 5.23	Inclusion efficiency values of all Freeze dried inclusion complexes, kneaded mixtures and physical mixtures of FBX with cyclodextrins (β -CD, HP- β -CD, M- β -CD and γ -CD) in 1:1, 1:2 and 1:3 molar ratios of FBX:CD.	278
Table 5.24	Statistical representation of % Cumulative drug release versus sampling time of FBX-P, FBX-M and Freeze dried FBX-IC in phosphate buffer pH-6.8 (PB), acetate buffer pH-4.5 (AB), 0.1N HCl and water.	286
Table 5.25	Comparison of various dissolution parameters of FBX-P, FBX-M and Freeze dried FBX-IC in phosphate buffer pH-6.8 (PB), acetate buffer pH-4.5 (AB), 0.1N HCl and water.	286
Table 5.26	Chemical stability (i.e. percentage drug content) of Freeze dried FBX-IC at different time intervals stored at $5^{\circ}\text{C}\pm 3^{\circ}\text{C}$ and room temperature.	287
Table 5.27	In vitro cytotoxicity studies of FBX-P and FBX-IC in Caco2 cell lines at 4 hours, 24 hours and 48 hours.	288
Table 5.28	IC ₅₀ values of FBX-P and FBX-IC in Caco2 cell lines at 4 hours, 24 hours and 48 hours.	288
Table 5.29	Apparent permeability coefficient (P_{app}) from apical to basolateral for FBX-P, FBX-M and FBX-IC using Caco-2 cells model.	290
Table 5.30	Statistical representation of FBX plasma profile for FBX-P, FBX-M and FBX-IC in Albino rabbits following oral administration.	292
Table 5.31	Pharmacokinetic parameters after oral administration of FBX-P, FBX-M and FBX-IC in Albino rabbits.	292