Chemical structure of Rifaximin

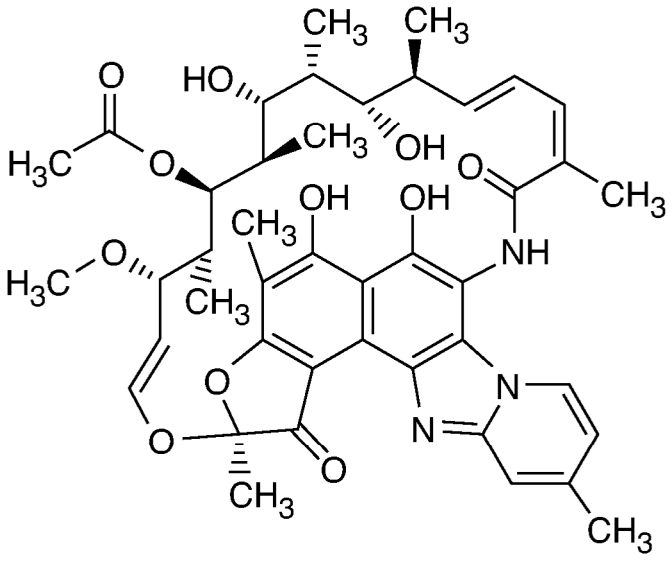


Fig. 1

Overlay of XRPD patterns for Rifaximin/PVP K-90 dispersions obtained from methanol by spray drying.

Top to bottom: 25:75 (w/w) Rifaximin/PVP K-90
50:75 (w/w) Rifaximin/PVP K-90
75:25 (w/w) Rifaximin/PVP K-90
Crystalline Rifaximin as-received

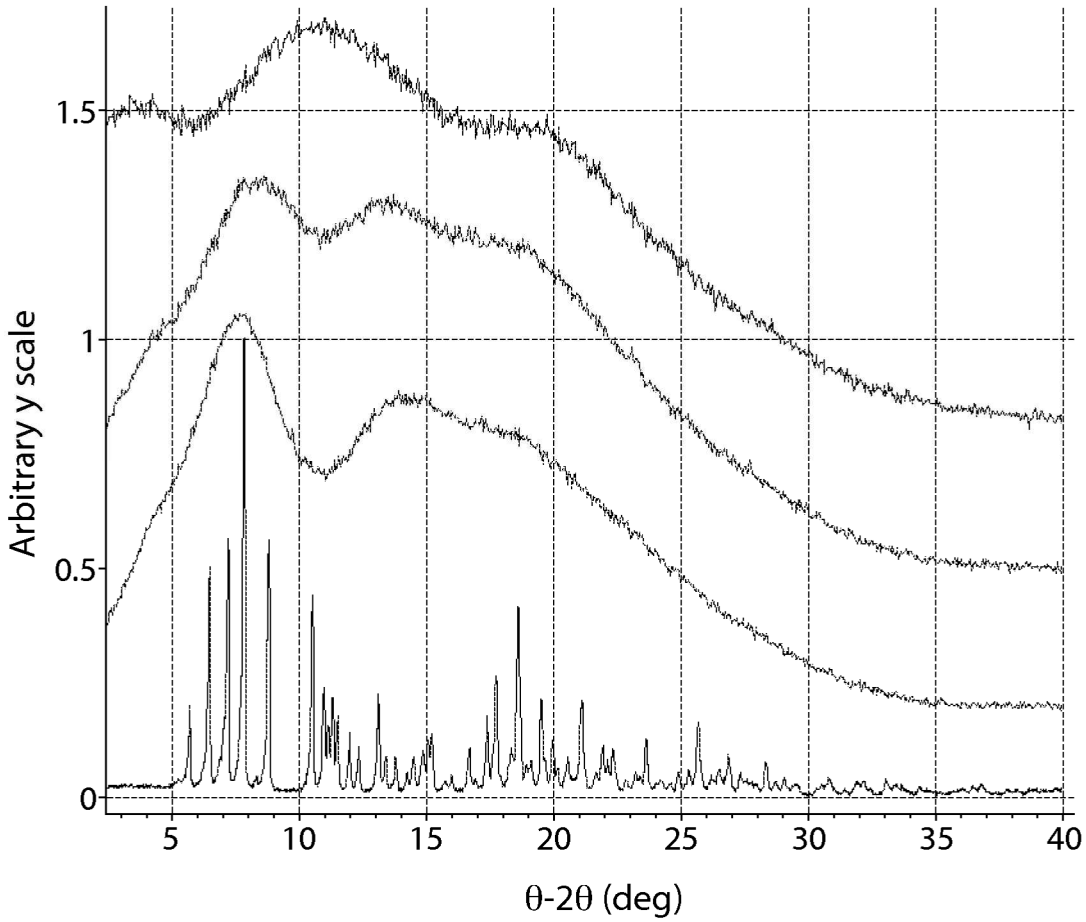


Fig. 2

mDSC thermogram for 25:75 (w/w) Rifaximin/PVP K-90 dispersion obtained from methanol by spray drying

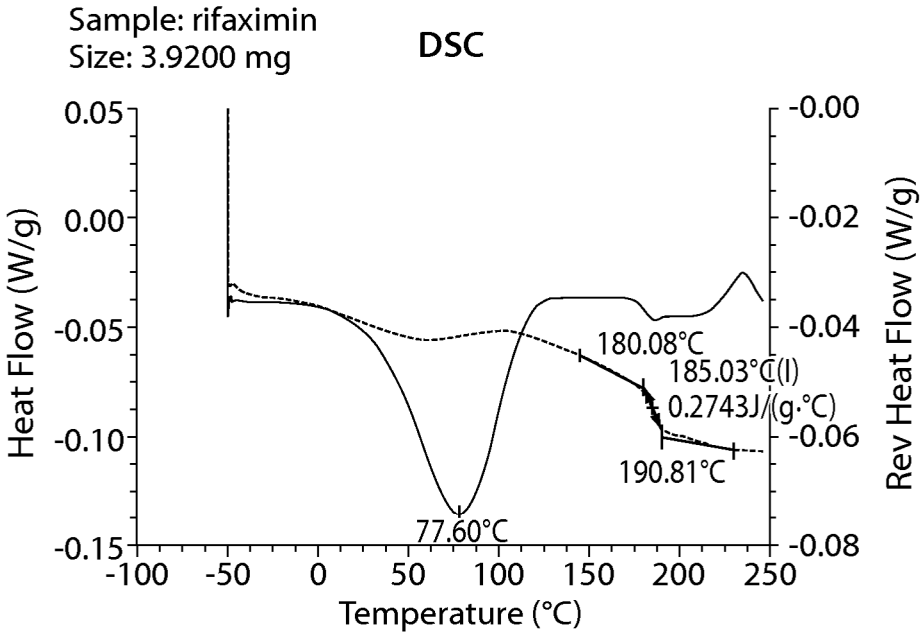


Fig. 3

mDSC thermogram for 50:50 (w/w) Rifaximin/PVP K-90 dispersion obtained from methanol by spray drying

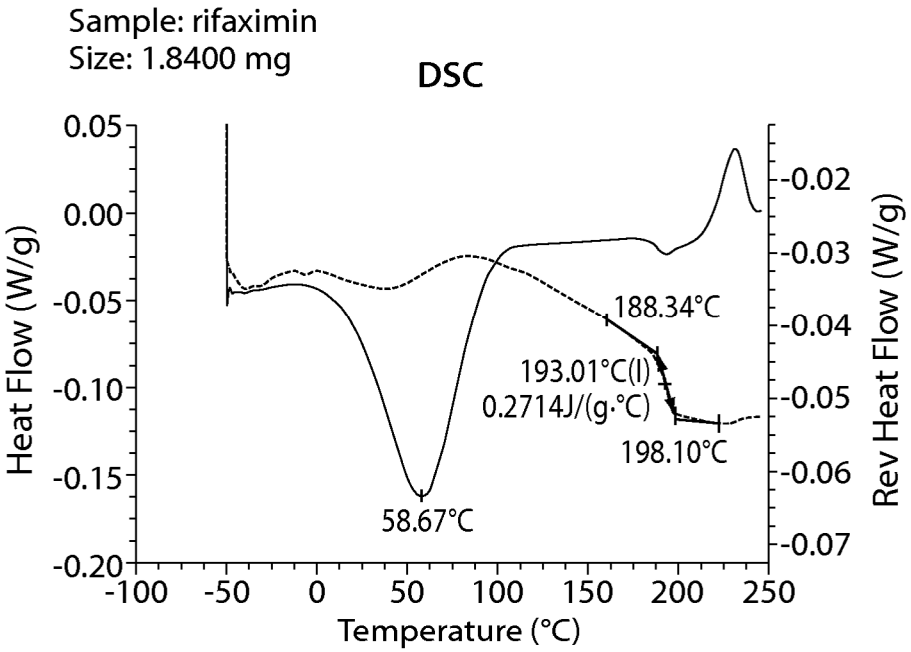


Fig. 4

mDSC thermogram for 75:25 (w/w) Rifaximin/PVP K-90 dispersion obtained from methanol by spray drying

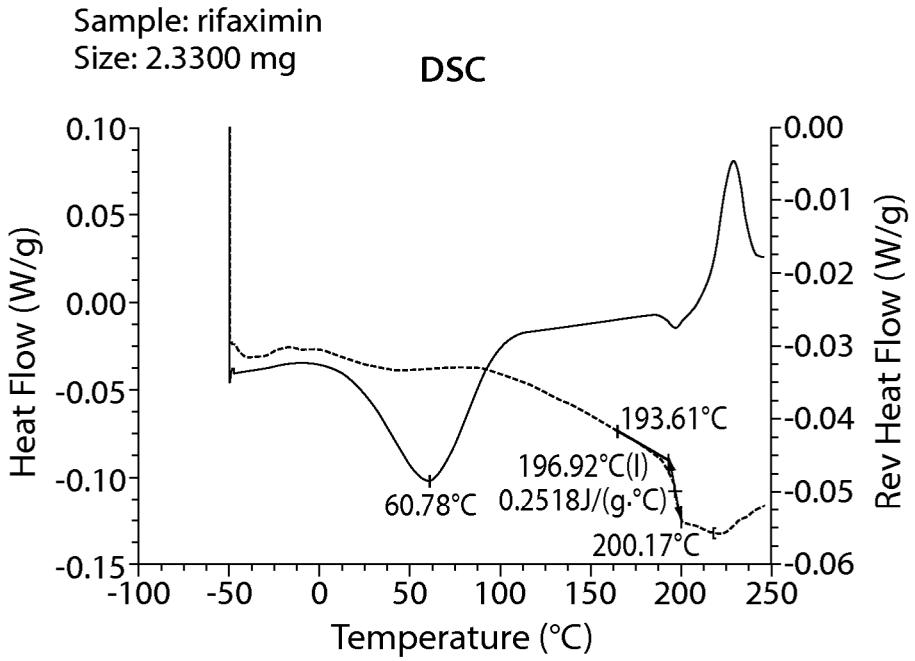


Fig. 5

Overlay of mDSC thermogram for Rifaximin/PVP K-90 dispersions obtained from methanol by spray drying.

Top to bottom: 25:75 (w/w) Rifaximin/PVP K-90
50:75 (w/w) Rifaximin/PVP K-90
75:25 (w/w) Rifaximin/PVP K-90

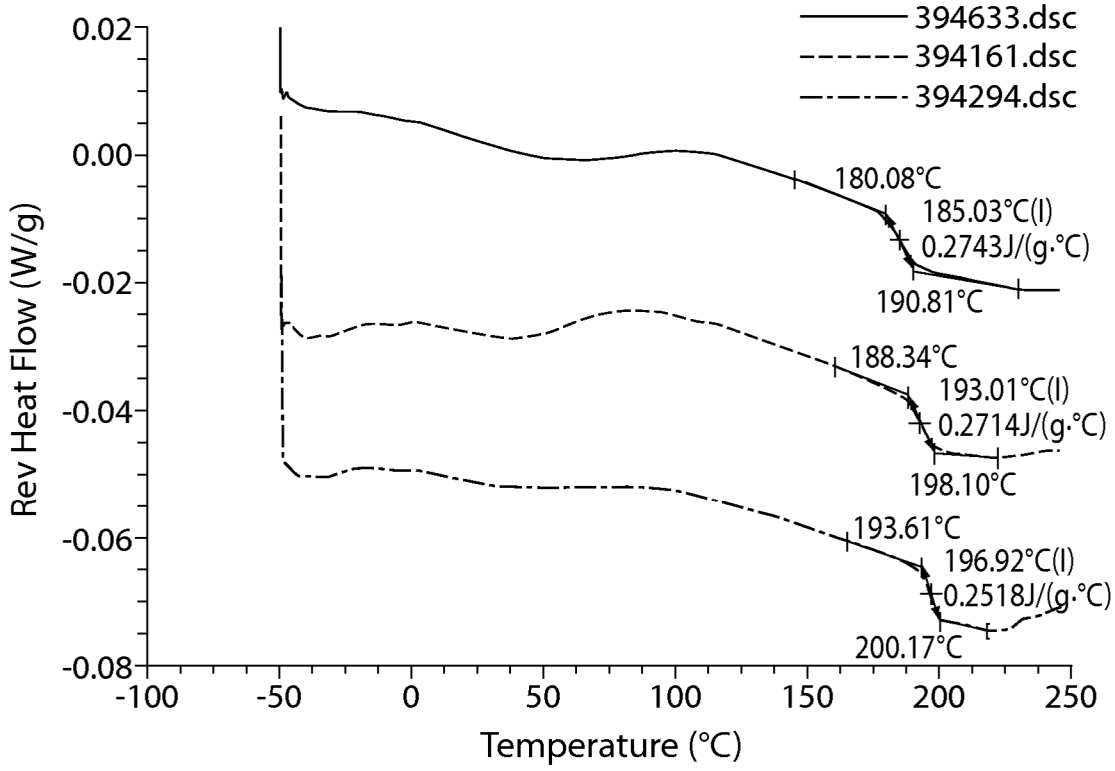


Fig. 6

Overlay of XRPD patterns for Rifaximin/HPMC-P dispersions obtained from methanol by spray drying.

Top to bottom: 25:75 (w/w) Rifaximin/HPMC-P
50:75 (w/w) Rifaximin/HPMC-P
75:25 (w/w) Rifaximin/HPMC-P
Crystalline Rifaximin as-received

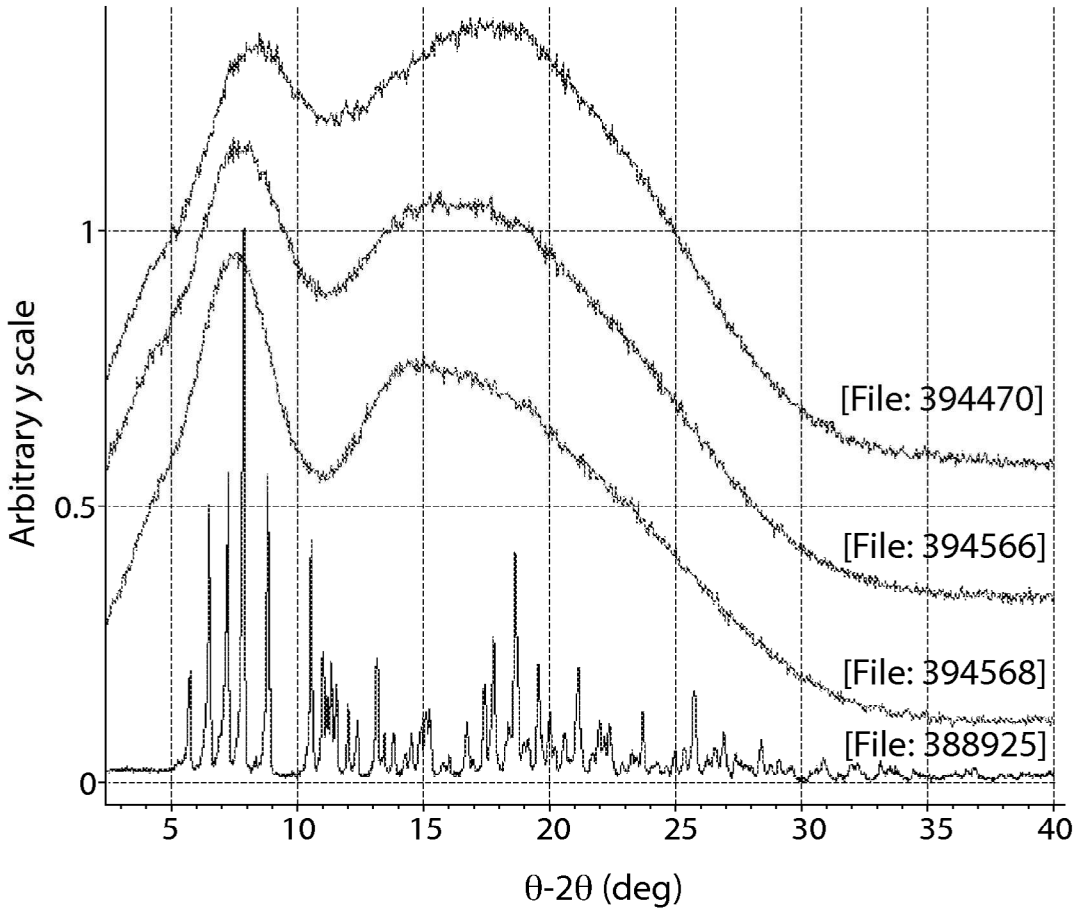


Fig. 7

mDSC thermogram for 25:75 (w/w) Rifaximin/HPMC-P dispersion obtained from methanol by spray drying

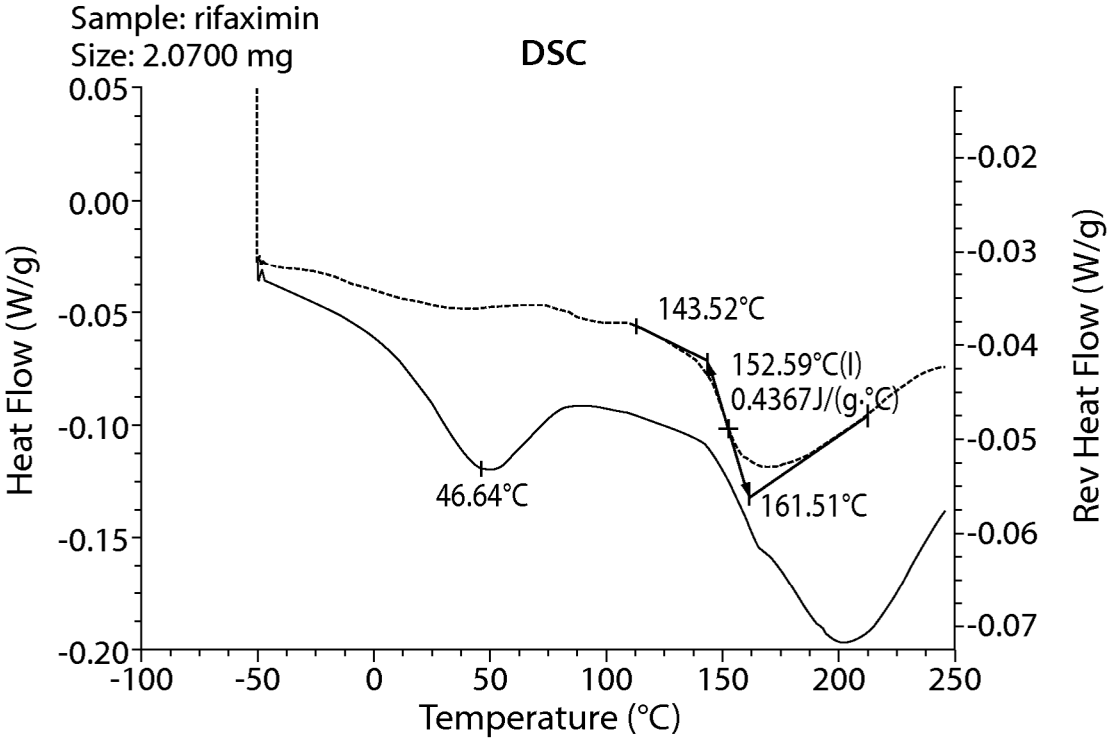


Fig. 8

mDSC thermogram for 50:50 (w/w) Rifaximin/HPMC-P dispersion obtained from methanol by spray drying

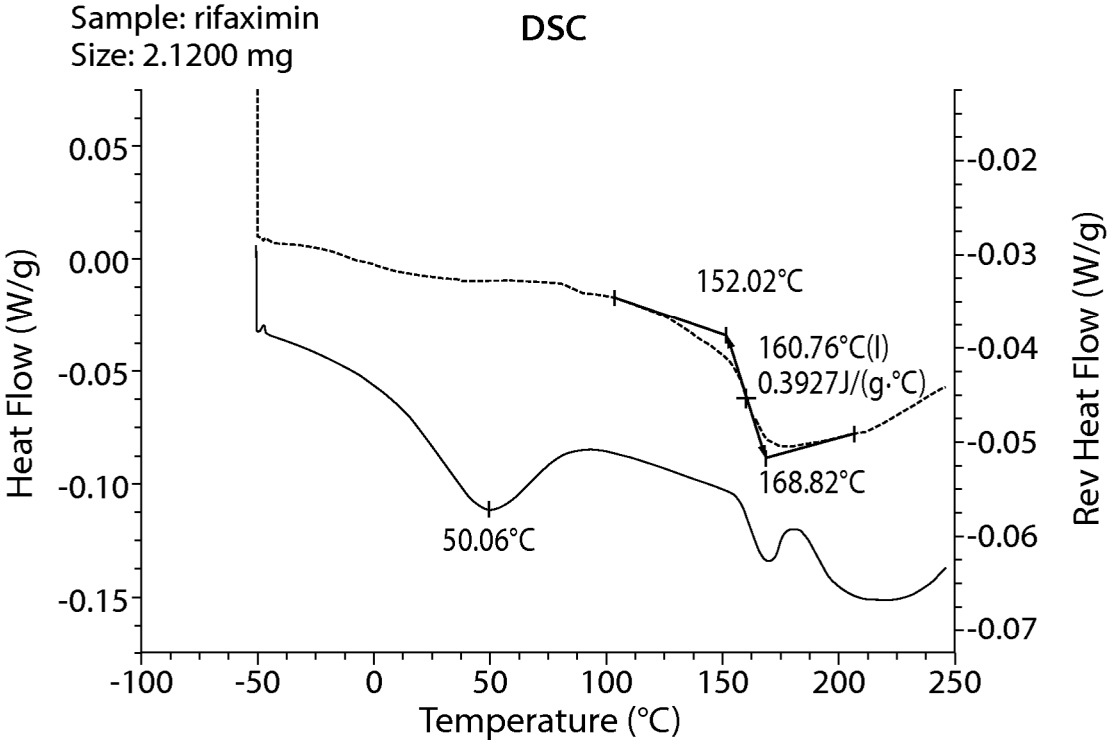


Fig. 9

mDSC thermogram for 75:25 (w/w) Rifaximin/HPMC-P dispersion obtained from methanol by spray drying

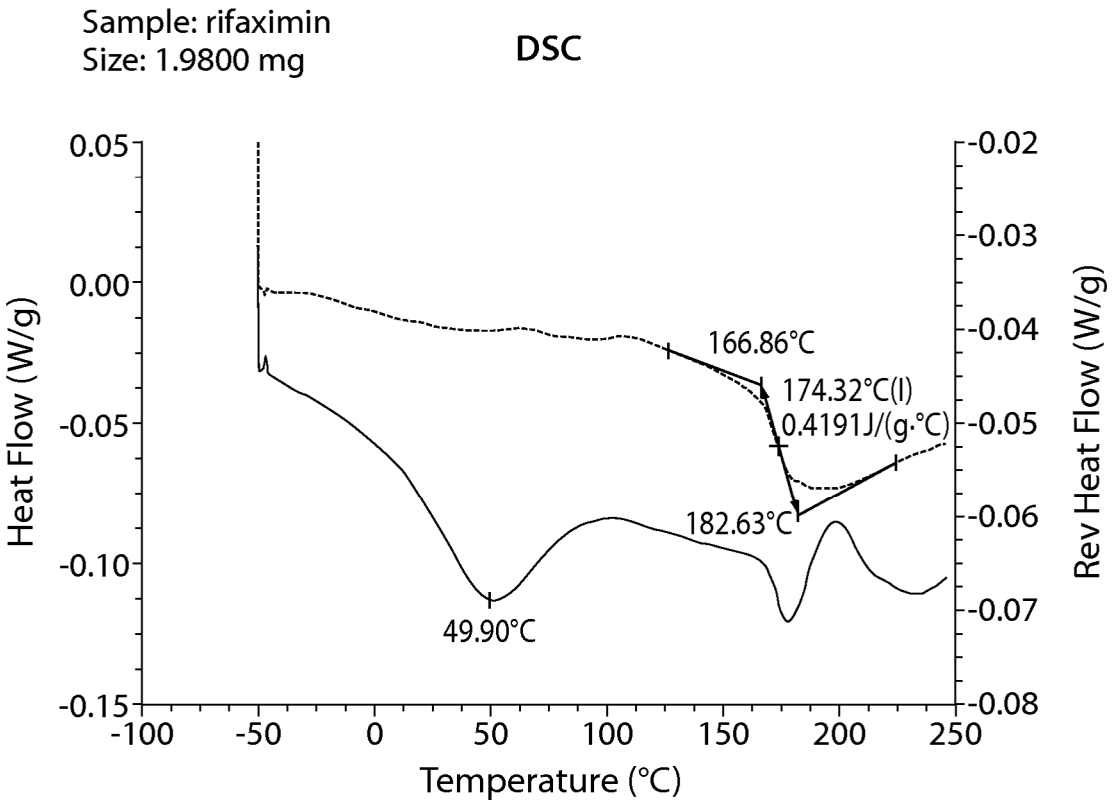


Fig. 10

Overlay of mDSC thermogram for Rifaximin/HPMC-P K-90 dispersions obtained from methanol by spray drying.

Top to bottom: 25:75 (w/w) Rifaximin/HPMC-P
50:75 (w/w) Rifaximin/HPMC-P
75:25 (w/w) Rifaximin/HPMC-P

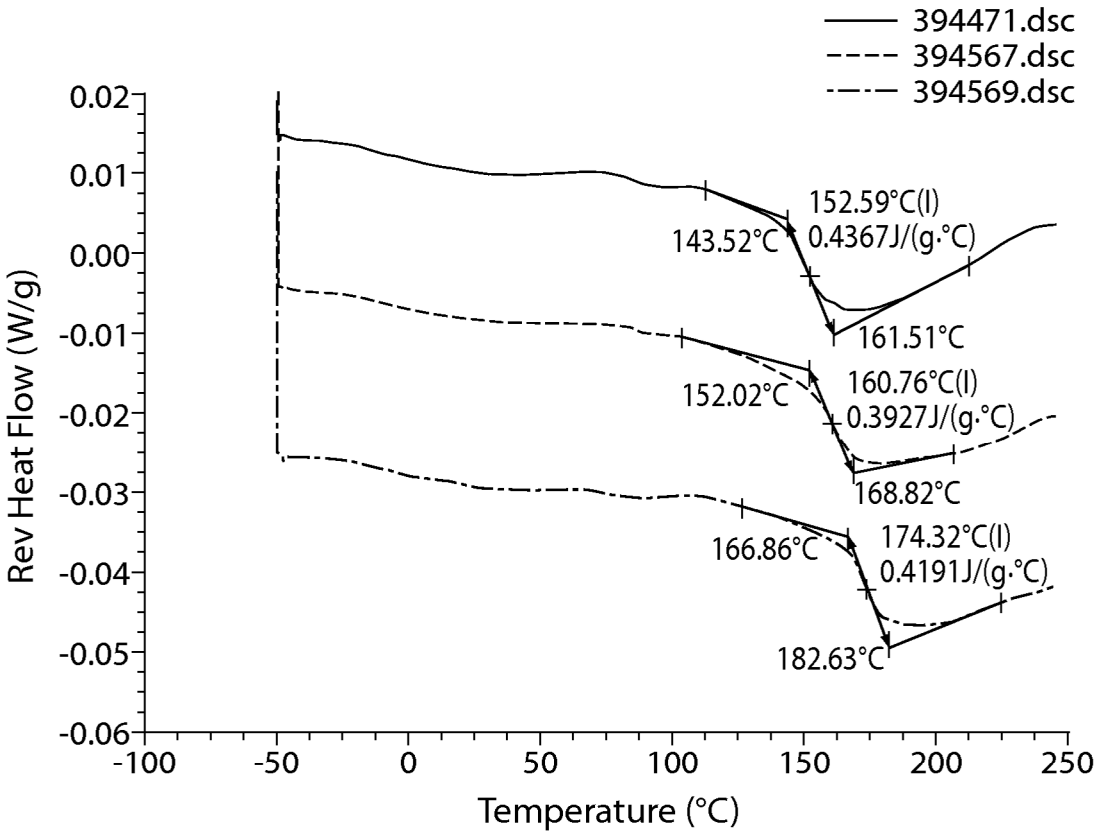


Fig. 11

Overlay of XRPD patterns for Rifaximin/HPMC-AS HG dispersions obtained from methanol by spray drying.

Top to bottom: 25:75 (w/w) Rifaximin/HPMC-AS HG
50:75 (w/w) Rifaximin/HPMC-AS HG
75:25 (w/w) Rifaximin/HPMC-AS HG
Crystalline Rifaximin as-received

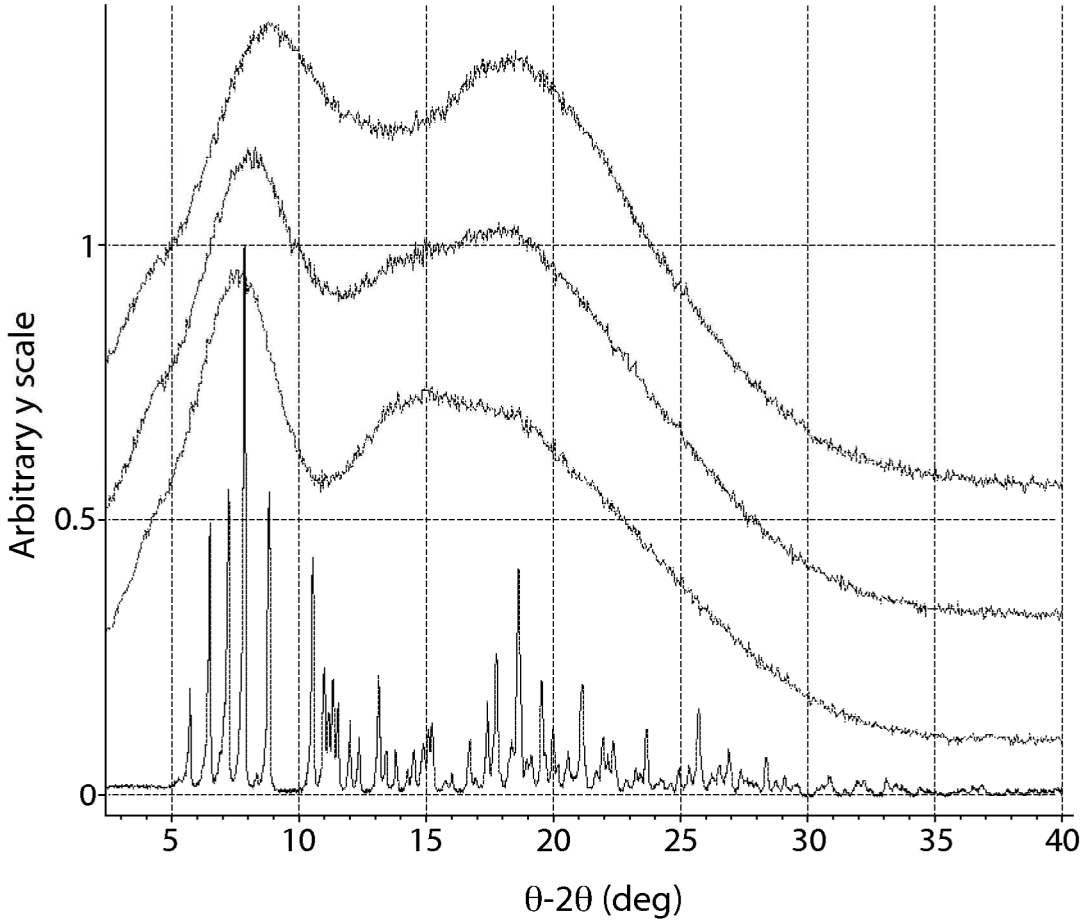


Fig. 12

mDSC thermogram for 25:75 (w/w) Rifaximin/HPMC-AS HG dispersion obtained from methanol by spray drying

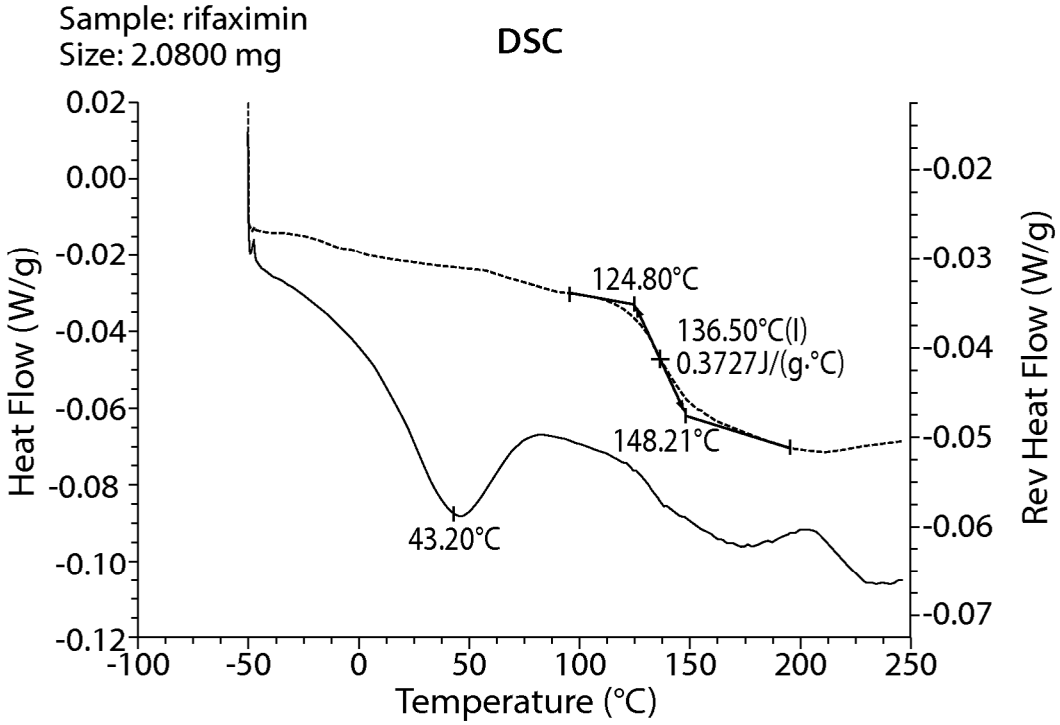


Fig. 13

mDSC thermogram for 50:50 (w/w) Rifaximin/HPMC-AS HG dispersion obtained from methanol by spray drying

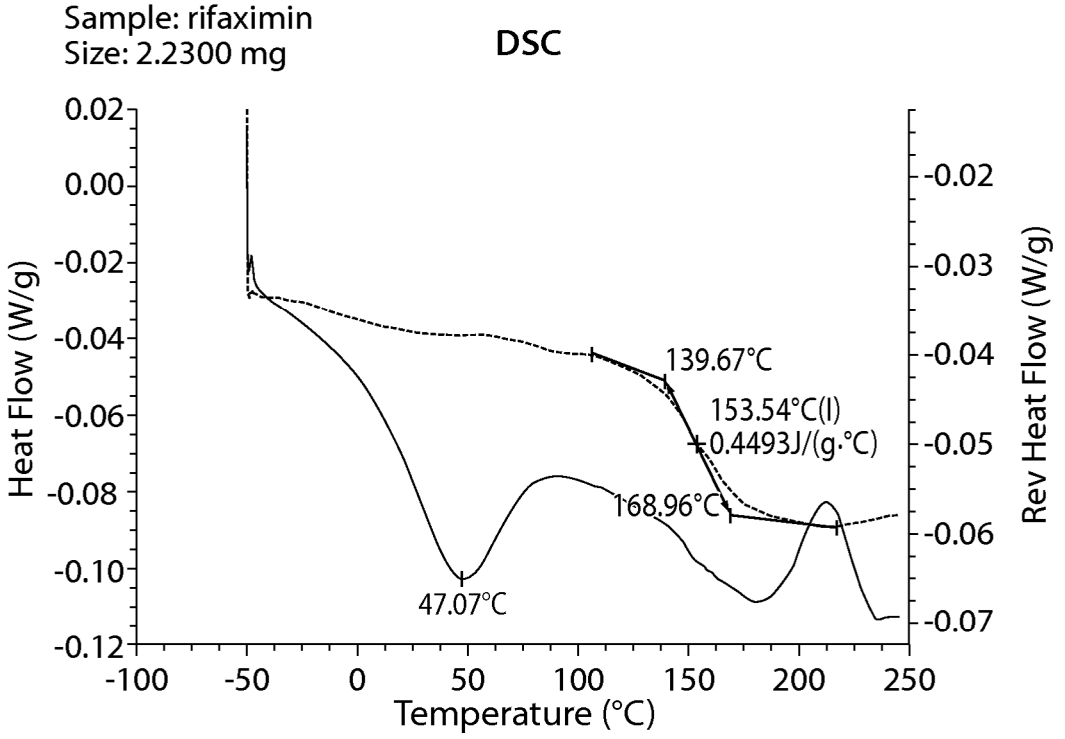


Fig. 14

mDSC thermogram for 75:25 (w/w) Rifaximin/HPMC-AS HG dispersion obtained from methanol by spray drying

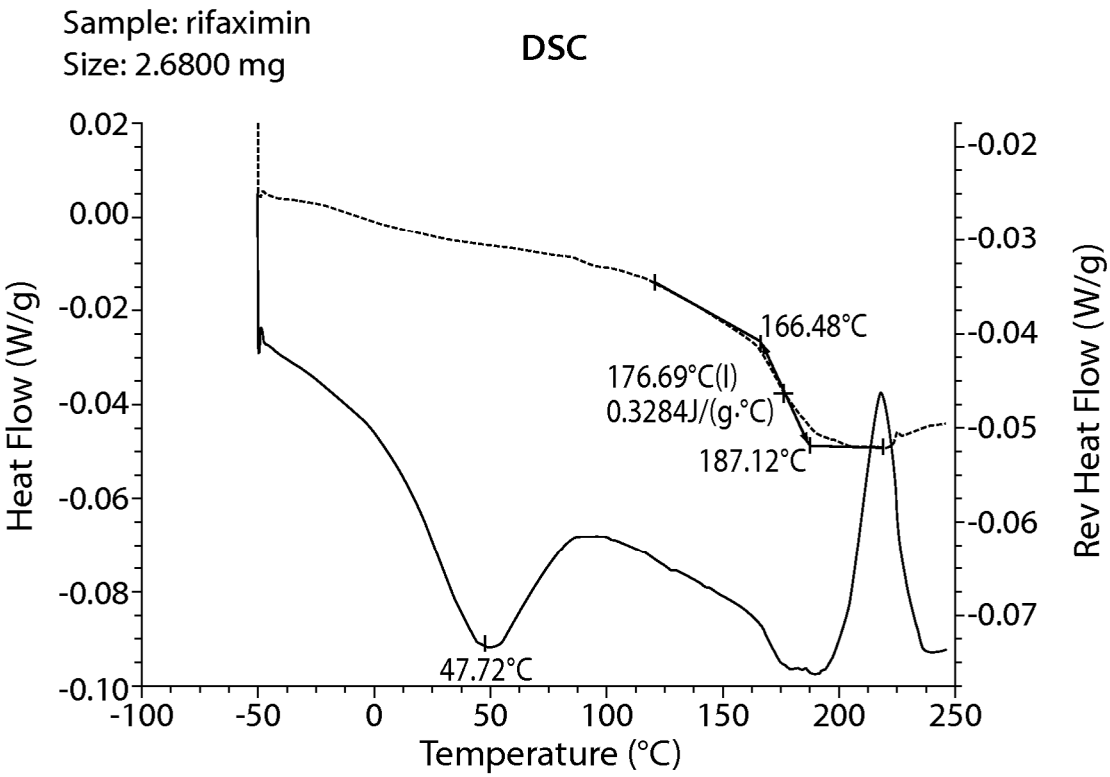


Fig. 15

Overlay of mDSC thermogram dor Rifaximin/HPMC-AS HG dispersions obtained from methanol by spray drying.

Top to bottom: 25:75 (w/w) Rifaximin/HPMC-AS HG
50:75 (w/w) Rifaximin/HPMC-AS HG
75:25 (w/w) Rifaximin/HPMC-AS HG

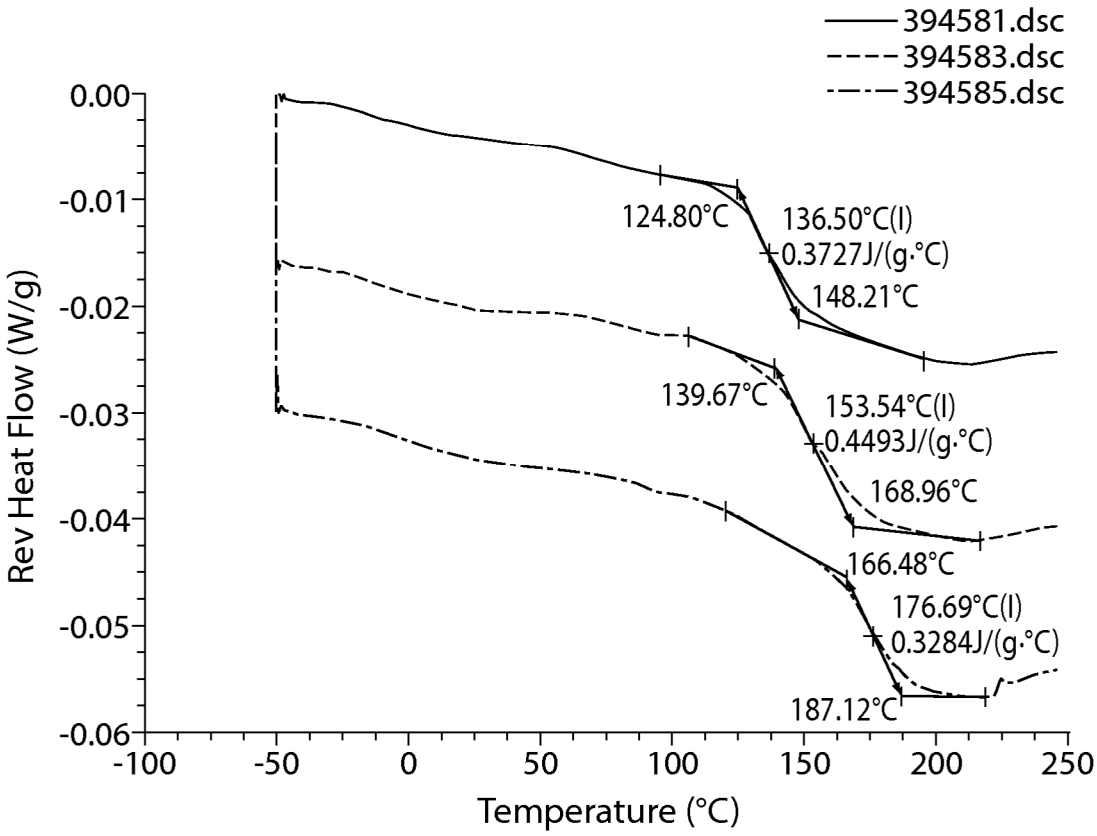


Fig. 16

Overlay of XRPD patterns for Rifaximin/HPMC-AS MG dispersions obtained from methanol by spray drying

Top to bottom: 25:75 (w/w) Rifaximin/HPMC-AS MG
50:75 (w/w) Rifaximin/HPMC-AS MG
75:25 (w/w) Rifaximin/HPMC-AS MG
Crystalline Rifaximin as-received

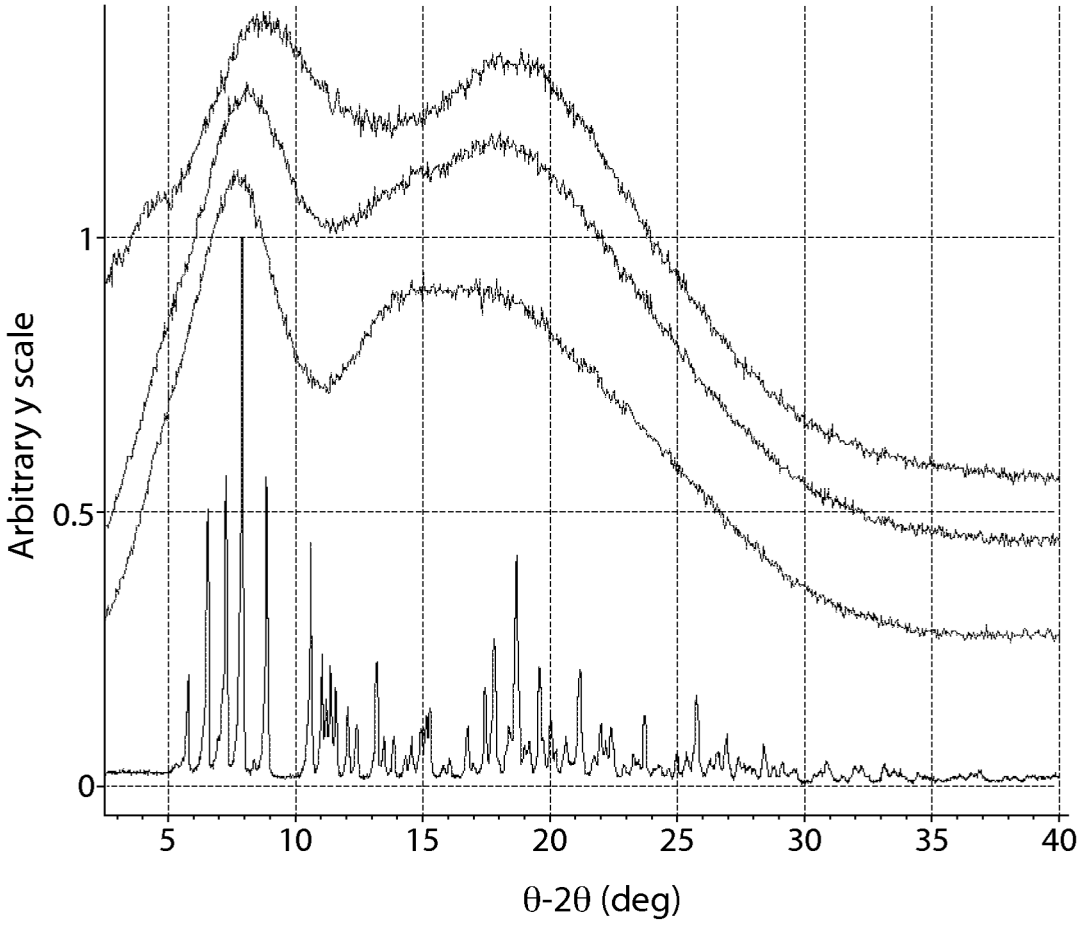


Fig. 17

mDSC thermogram for 25:75 (w/w) Rifaximin/HPMC-AS MG dispersion obtained from methanol by spray drying

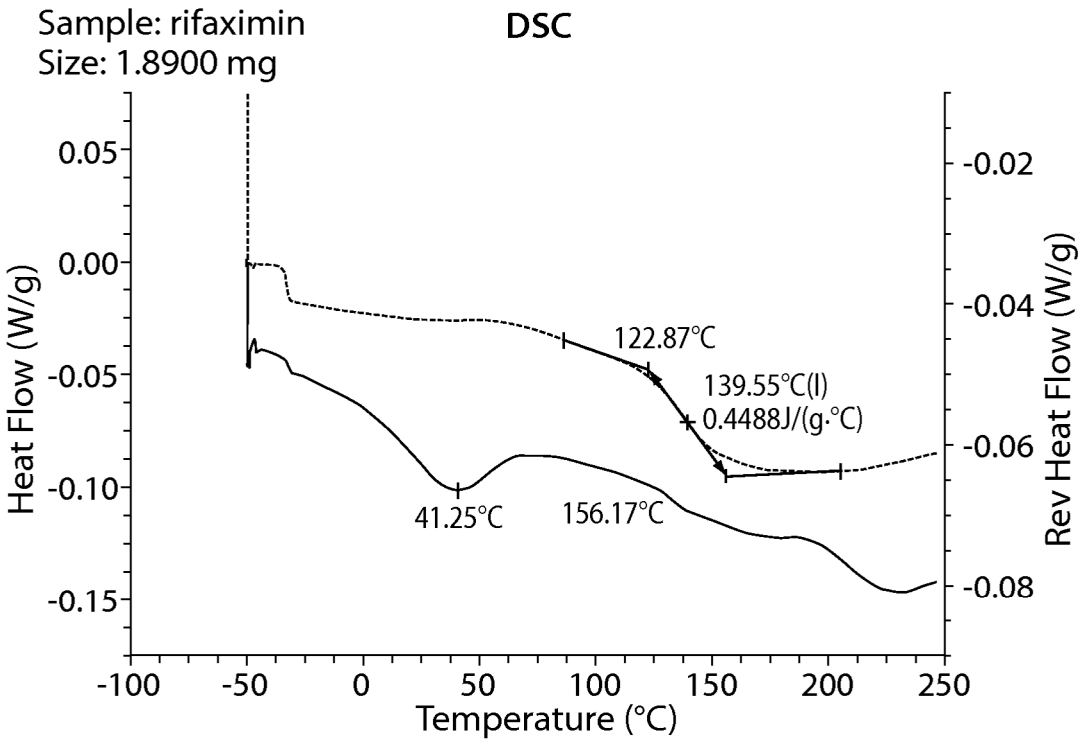


Fig. 18

mDSC thermogram for 50:50 (w/w) Rifaximin/HPMC-AS MG dispersion obtained from methanol by spray drying

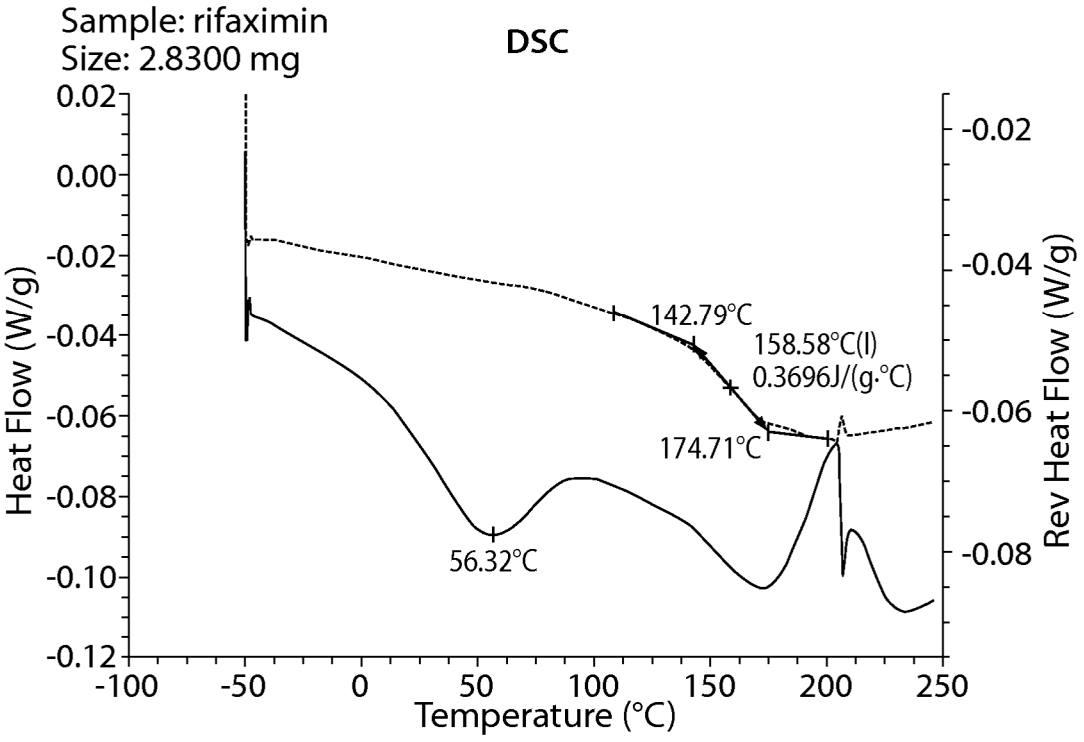


Fig. 19

mDSC thermogram for 75:25 (w/w) Rifaximin/HPMC-AS MG dispersion obtained from methanol by spray drying

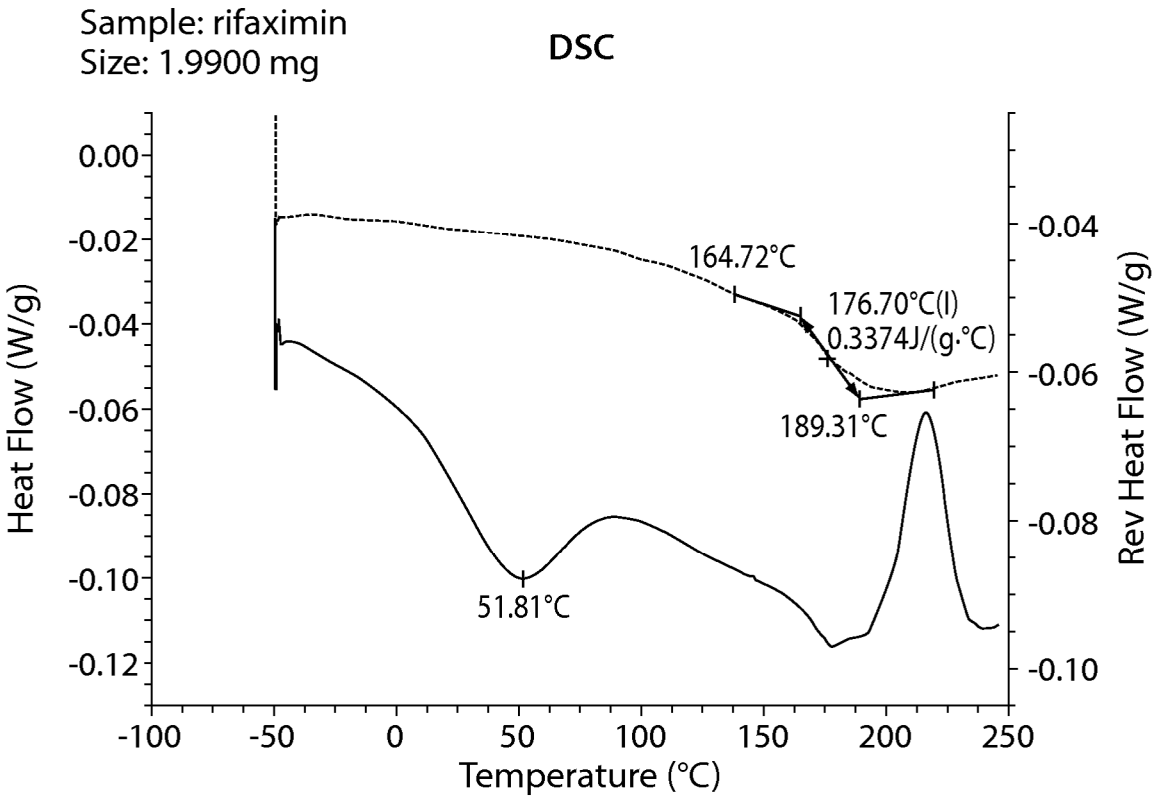


Fig. 20

Overlay of mDSC thermogram for Rifaximin/HPMC-AS MG dispersions obtained from methanol by spray drying.

Top to bottom: 25:75 (w/w) Rifaximin/HPMC-AS MG
50:75 (w/w) Rifaximin/HPMC-AS MG
75:25 (w/w) Rifaximin/HPMC-AS MG

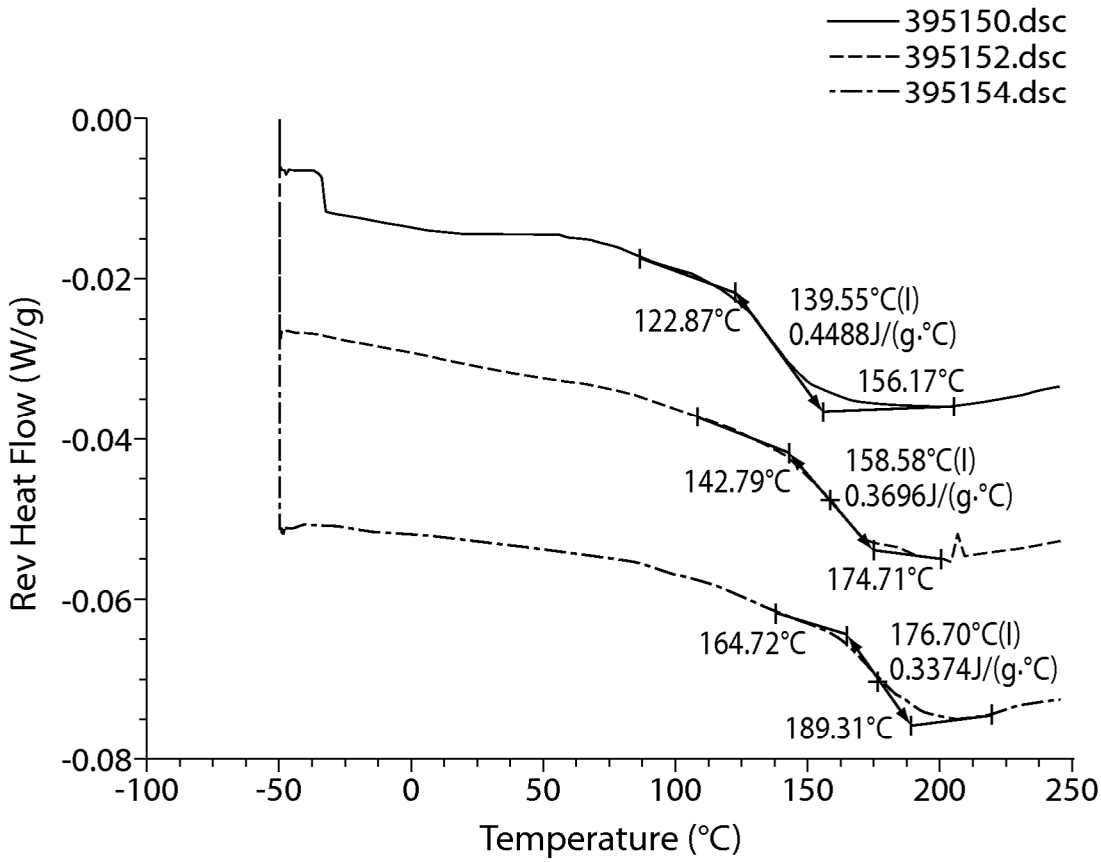


Fig. 21

Overlay of XRPD patterns for Rifaximin/Eudragit L100-55 dispersions obtained from methanol by spray drying.

Top to bottom: 25:75 (w/w) Rifaximin/Eudragit L100-55
50:75 (w/w) Rifaximin/Eudragit L100-55
75:25 (w/w) Rifaximin/Eudragit L100-55
Crystalline Rifaximin as-received

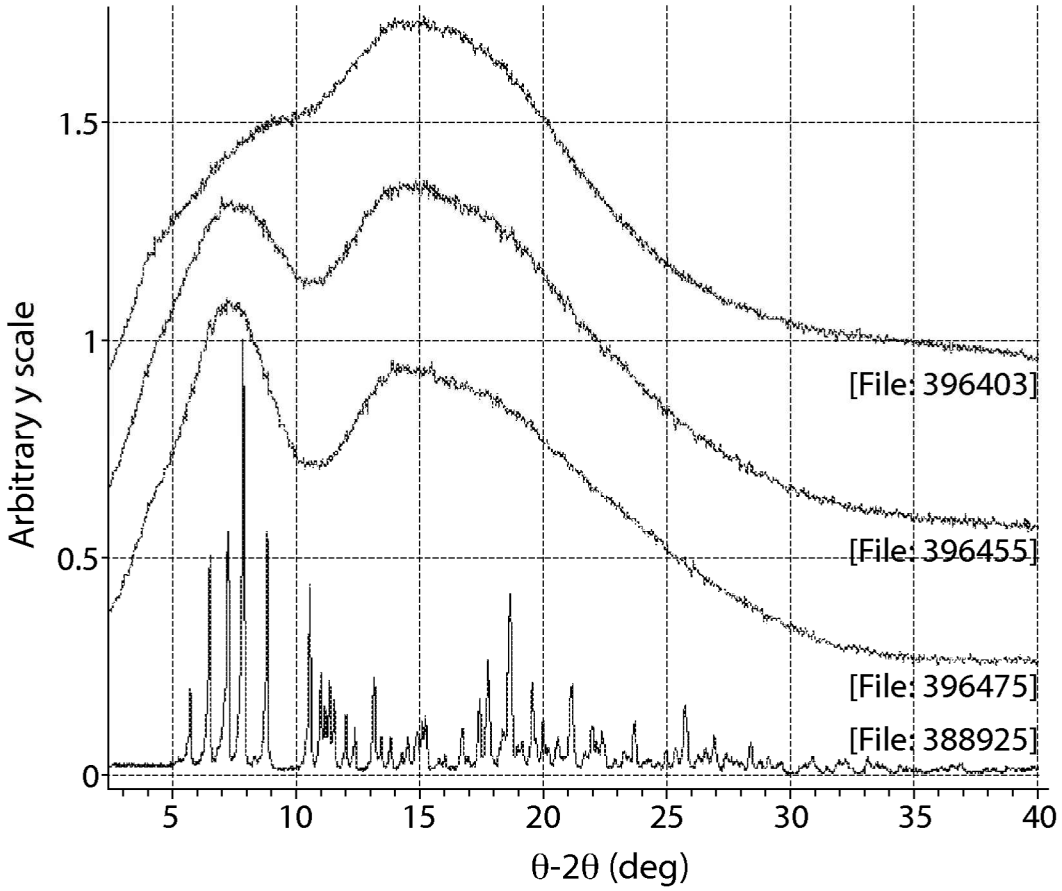


Fig. 22

mDSC thermogram for 25:75 (w/w) Rifaximin/Eudragit L100-55 dispersion obtained from methanol by spray drying

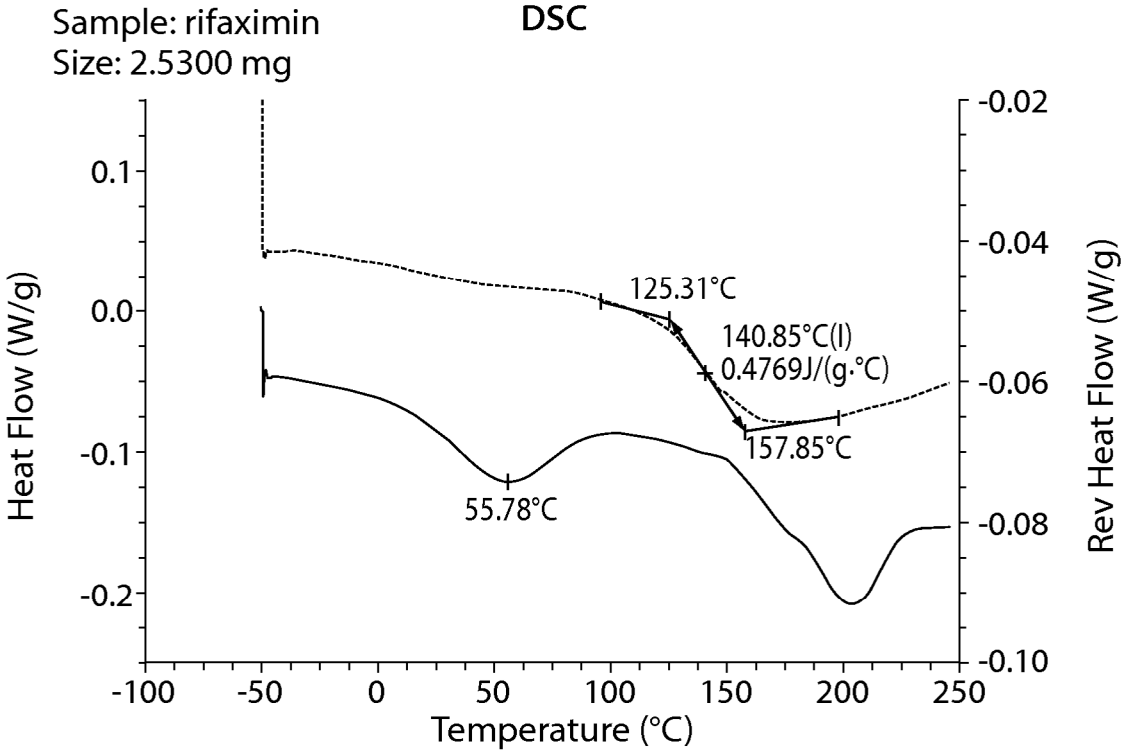


Fig. 23

mDSC thermogram for 50:50 (w/w) Rifaximin/Eudragit L100-55 dispersion obtained from methanol by spray drying

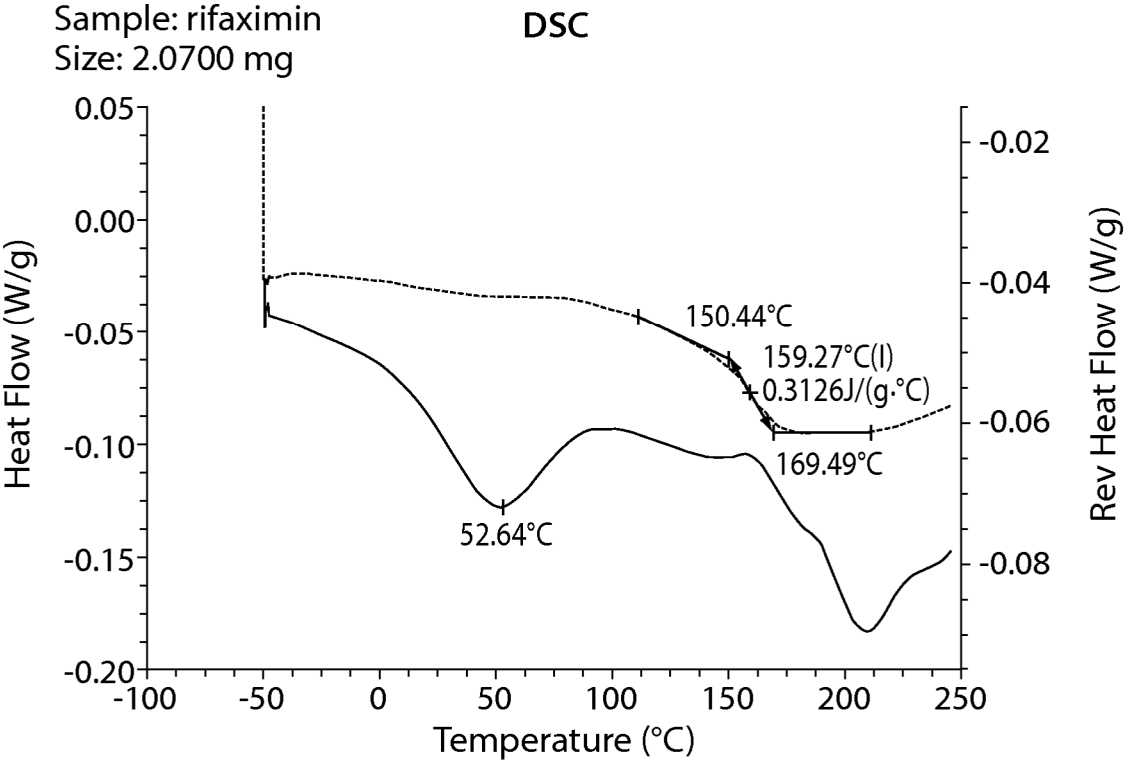


Fig. 24

mDSC thermogram for 75:25 (w/w) Rifaximin/Eudragit L100-55 dispersion obtained from methanol by spray drying

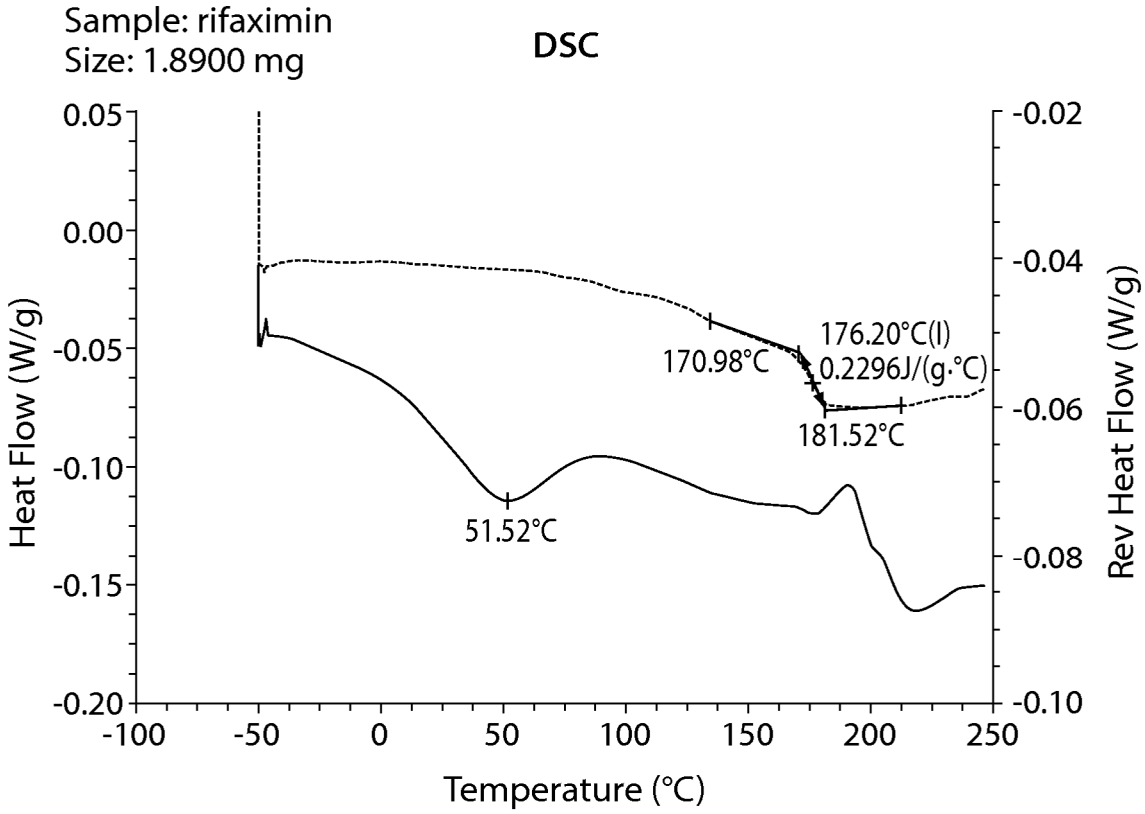


Fig. 25

Overlay of mDSC thermogram for Rifaximin/Eudragit L100-55 dispersions obtained from methanol by spray drying

Top to bottom: 25:75 (w/w) Rifaximin/Eudragit L100-55
50:75 (w/w) Rifaximin/Eudragit L100-55
75:25 (w/w) Rifaximin/Eudragit L100-55

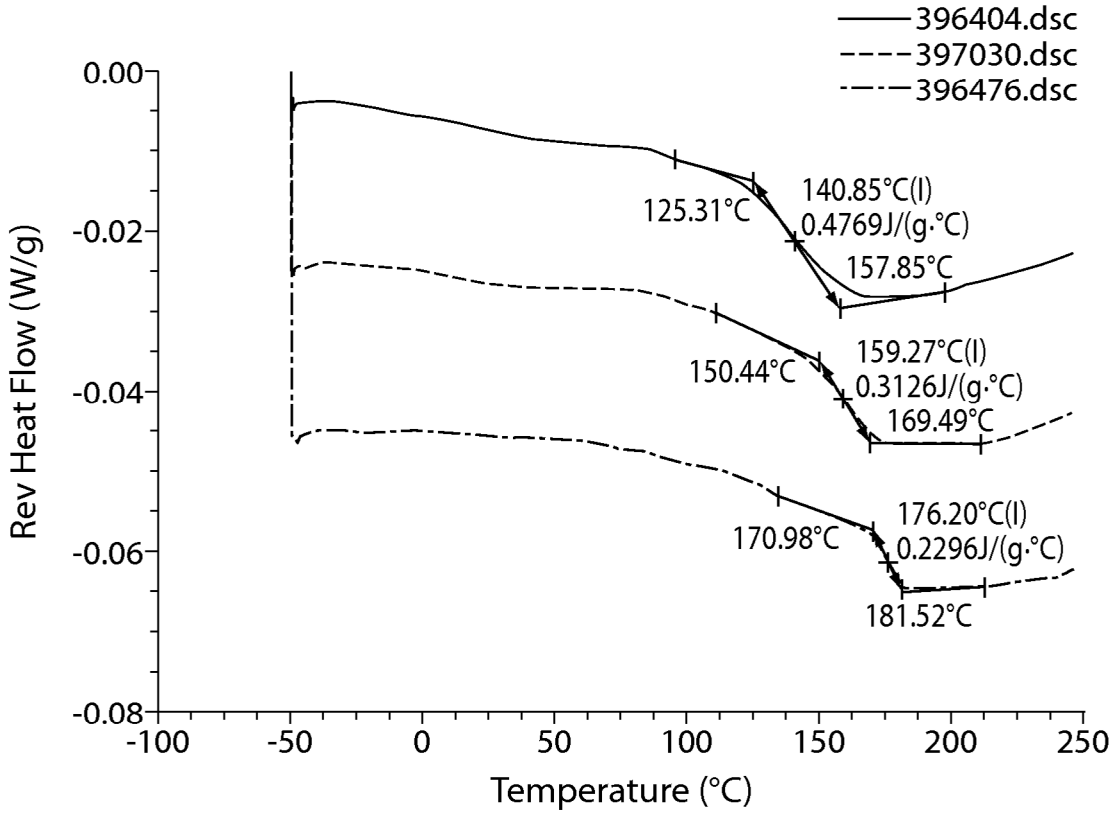


Fig. 26

mDSC thergram for 25:75 (w/w) Rifaximin/HPMC-P dispersion stressed at 40 °C/75% RH for 7 d

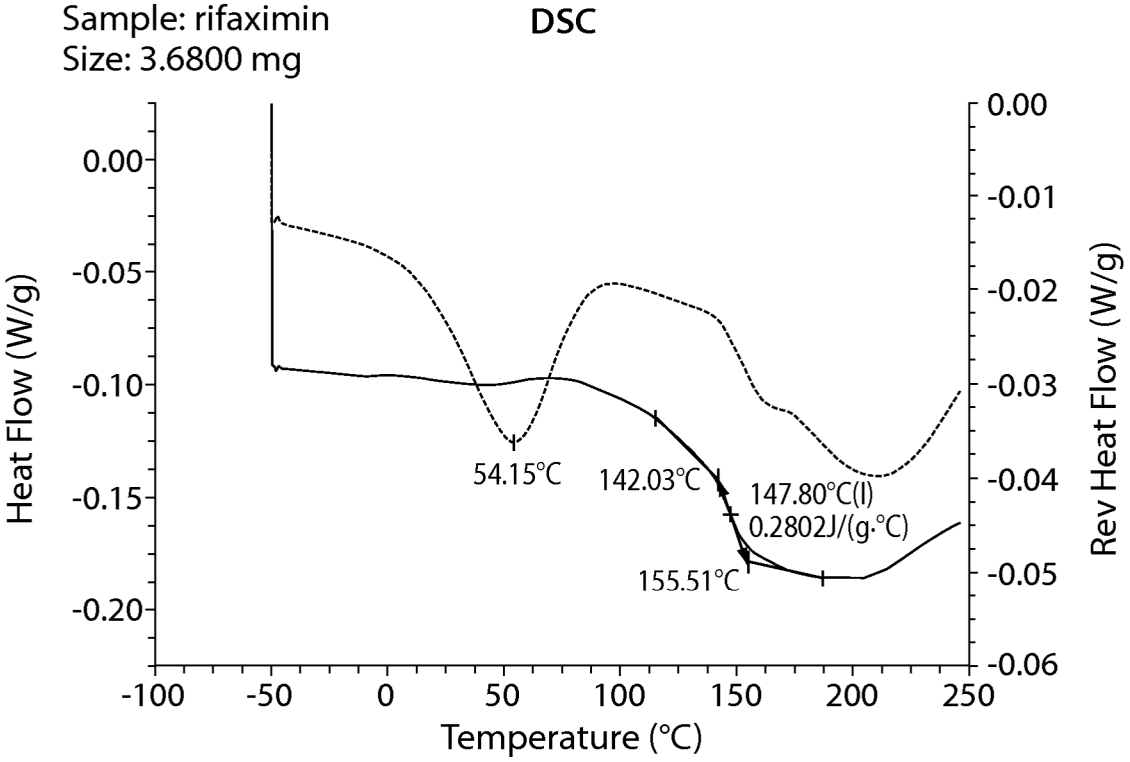


Fig. 27

mDSC thergram for 75:25 (w/w) Rifaximin/HPMC-AS HG dispersion stressed at 40 °C/75% RH for 7 d

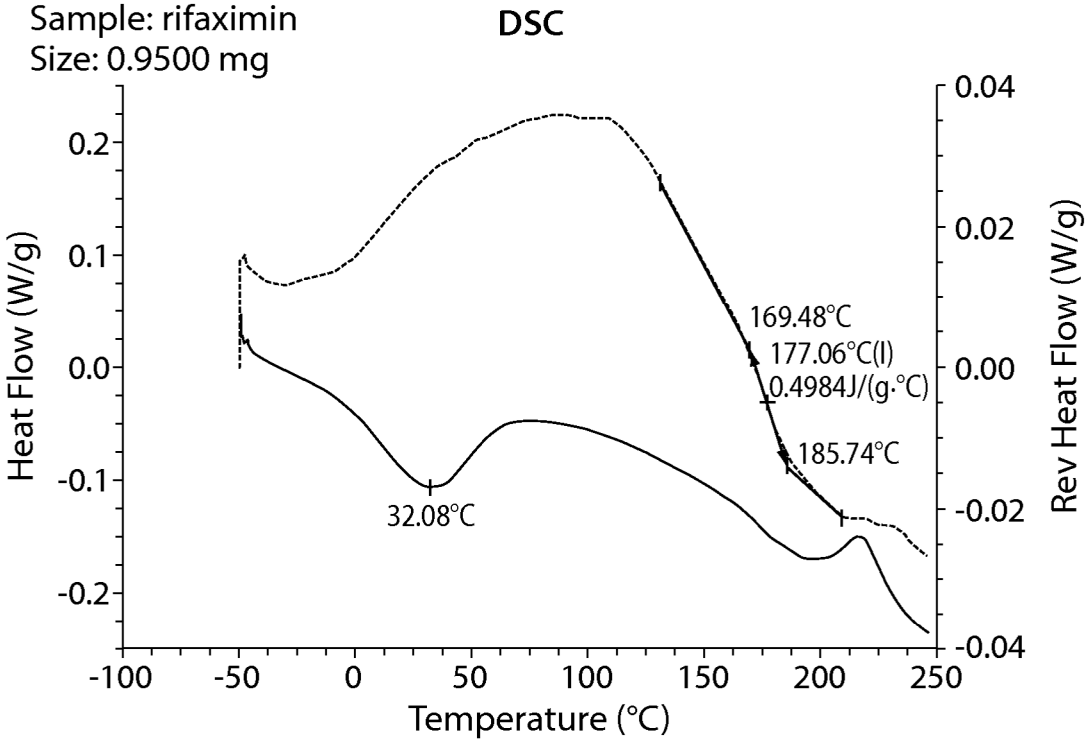


Fig. 28

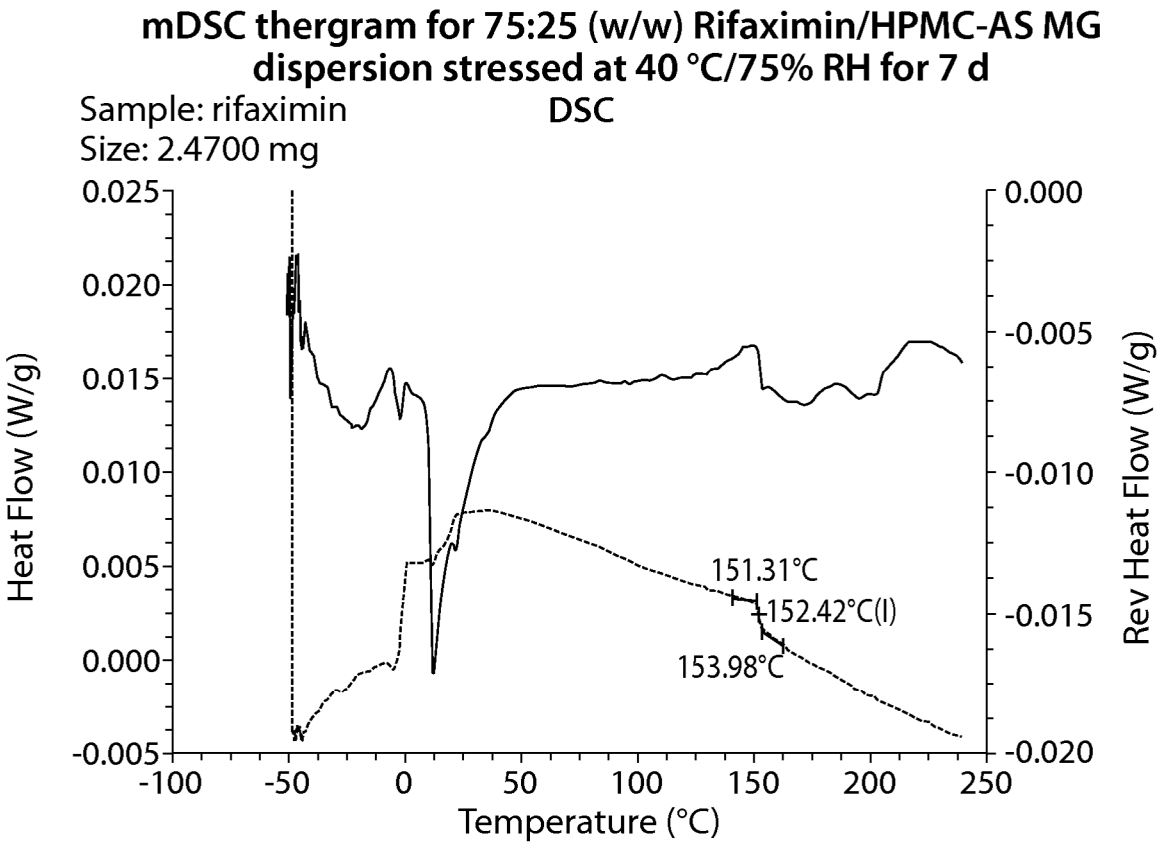

mDSC thergram for 75:25 (w/w) Rifaximin/HPMC-AS MG dispersion stressed at 40 °C/75% RH for 7 d
Sample: rifaximin
Size: 2.4700 mg
DSC
Heat Flow (W/g)
Rev Heat Flow (W/g)
Temperature (°C)
151.31°C
152.42°C(I)
153.98°C
0.025
0.020
0.015
0.010
0.005
0.000
-0.005
0.000
-0.005
-0.010
-0.015
-0.020
-100
-50
0
50
100
150
200
250

Fig. 29

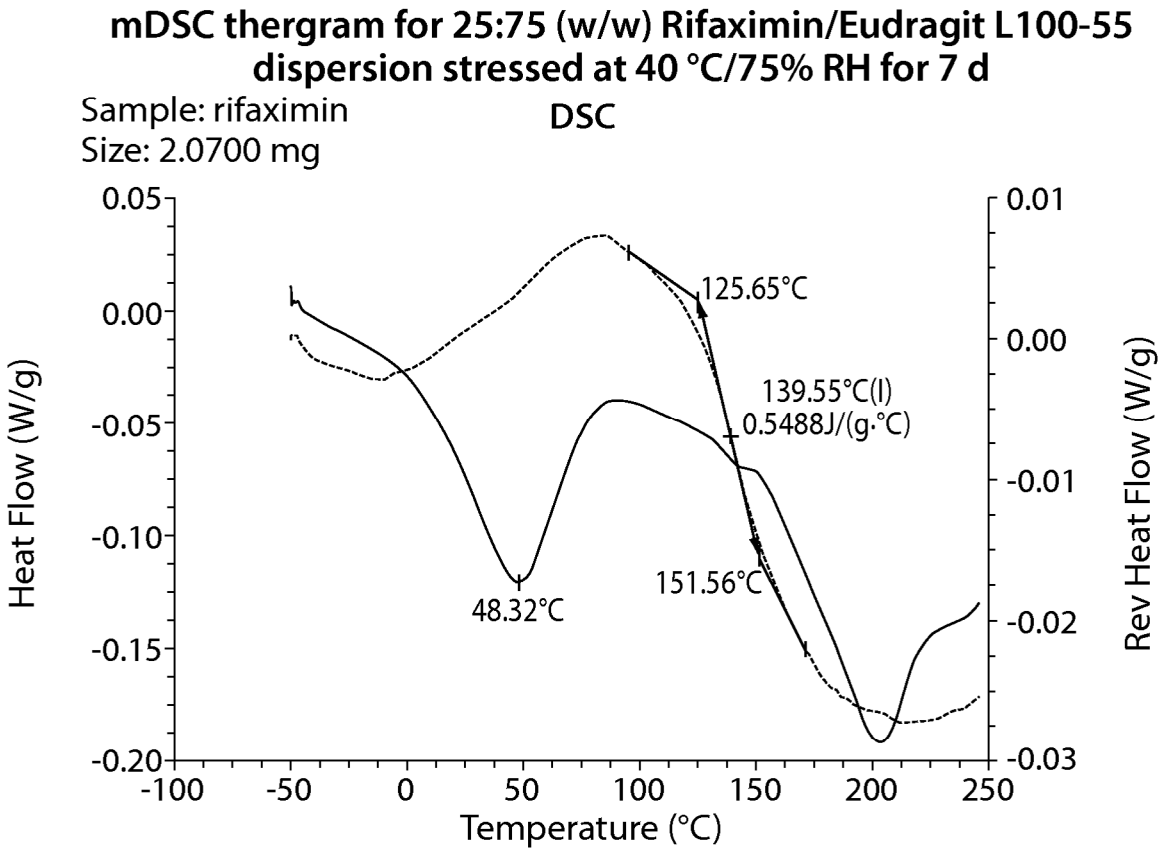

mDSC thergram for 25:75 (w/w) Rifaximin/Eudragit L100-55 dispersion stressed at 40 °C/75% RH for 7 d
Sample: rifaximin
Size: 2.0700 mg
DSC
Heat Flow (W/g)
Rev Heat Flow (W/g)
Temperature (°C)
125.65°C
139.55°C(I)
0.5488J/(g·°C)
48.32°C
151.56°C
0.05
0.00
-0.05
-0.10
-0.15
-0.20
0.01
0.00
-0.01
-0.02
-0.03
-100
-50
0
50
100
150
200
250

Fig. 30

XRPD pattern for 50:50 (w/w) Rifaximin/HPMC-AS MG dispersion

top: 50:50 (w/w) Rifaximin/HPMC-AS MG
bottom: Crystalline Rifaximin as-received

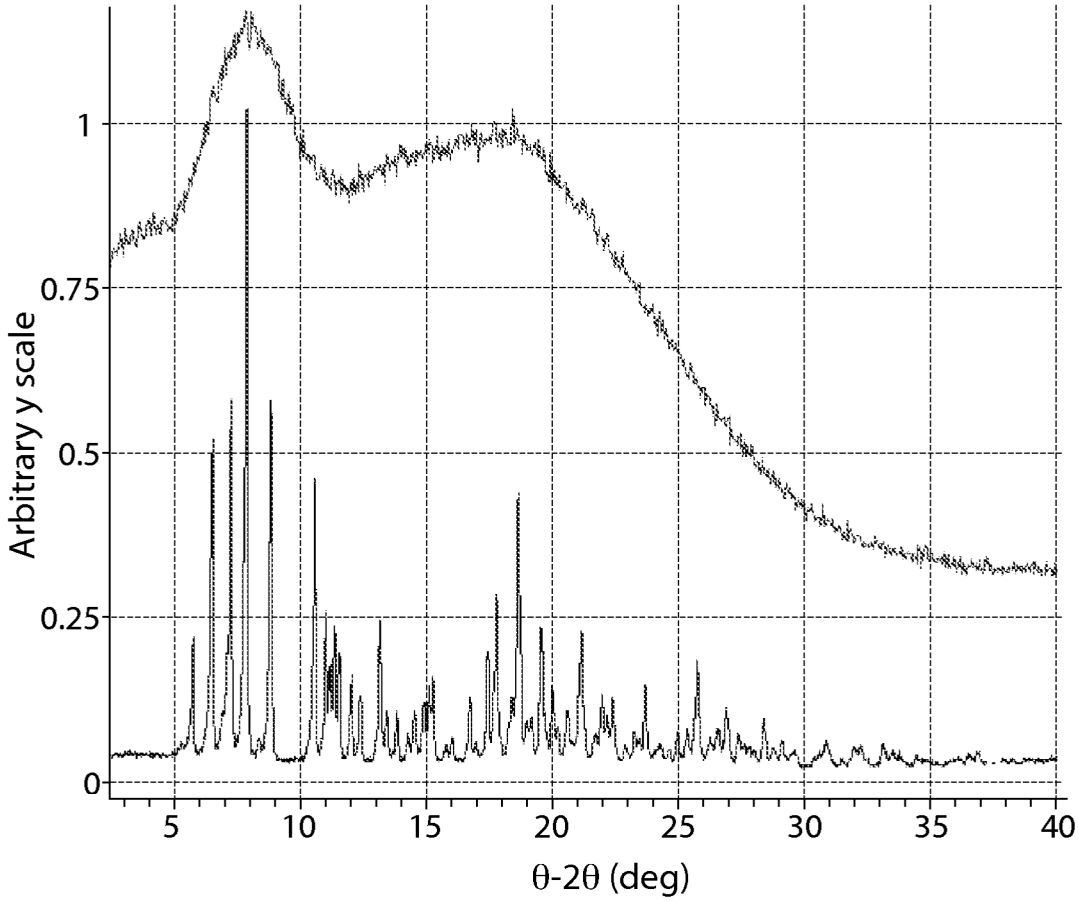


Fig. 31

Modulate DSC thermograms for 50:50 (w/w) Rifaximin/HPMC-AS MG dispersion

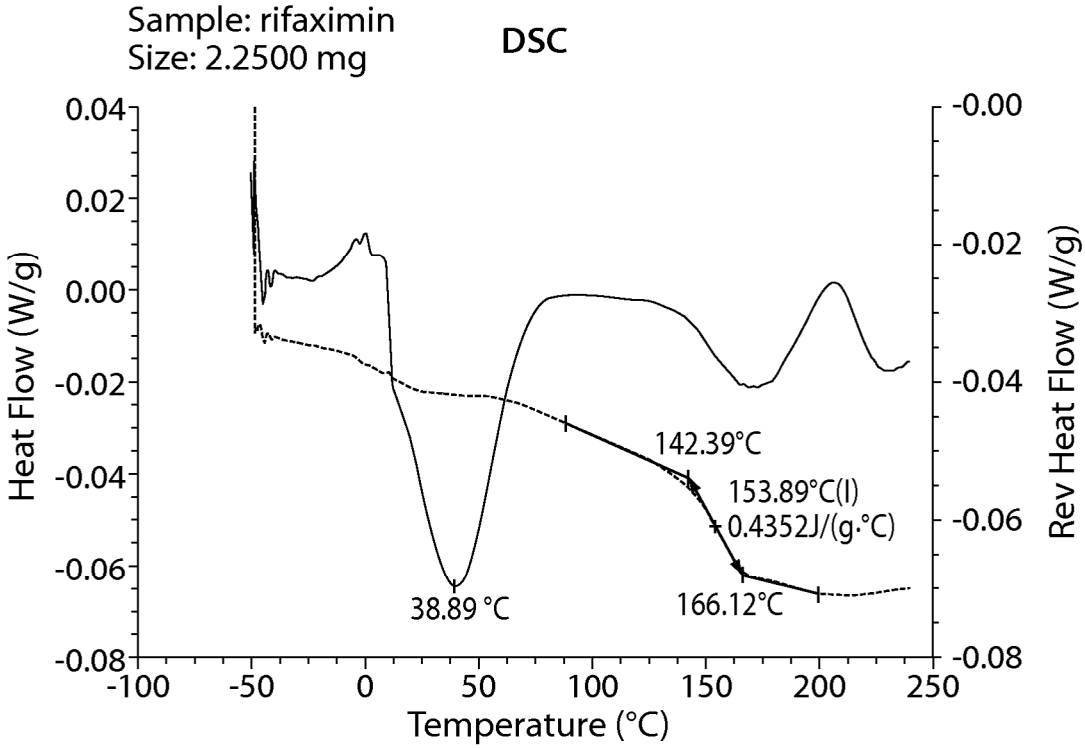


Fig. 32

TG-IR analysis for 50:50 (w/w) Rifaximin/HPMC-AS MG dispersion — TGA data

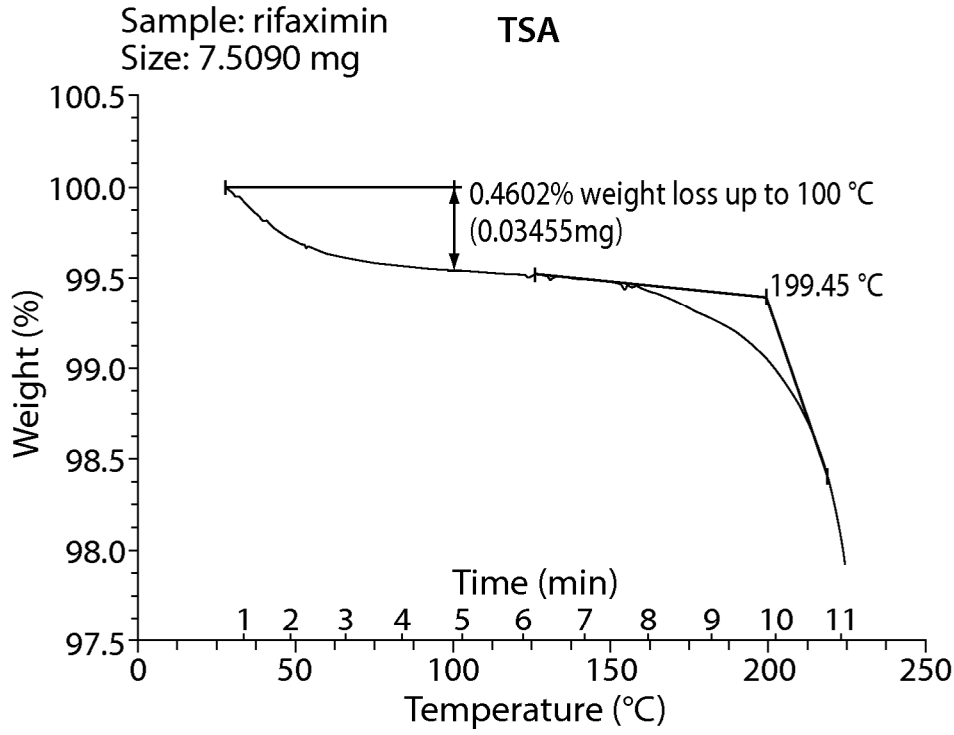


Fig. 33

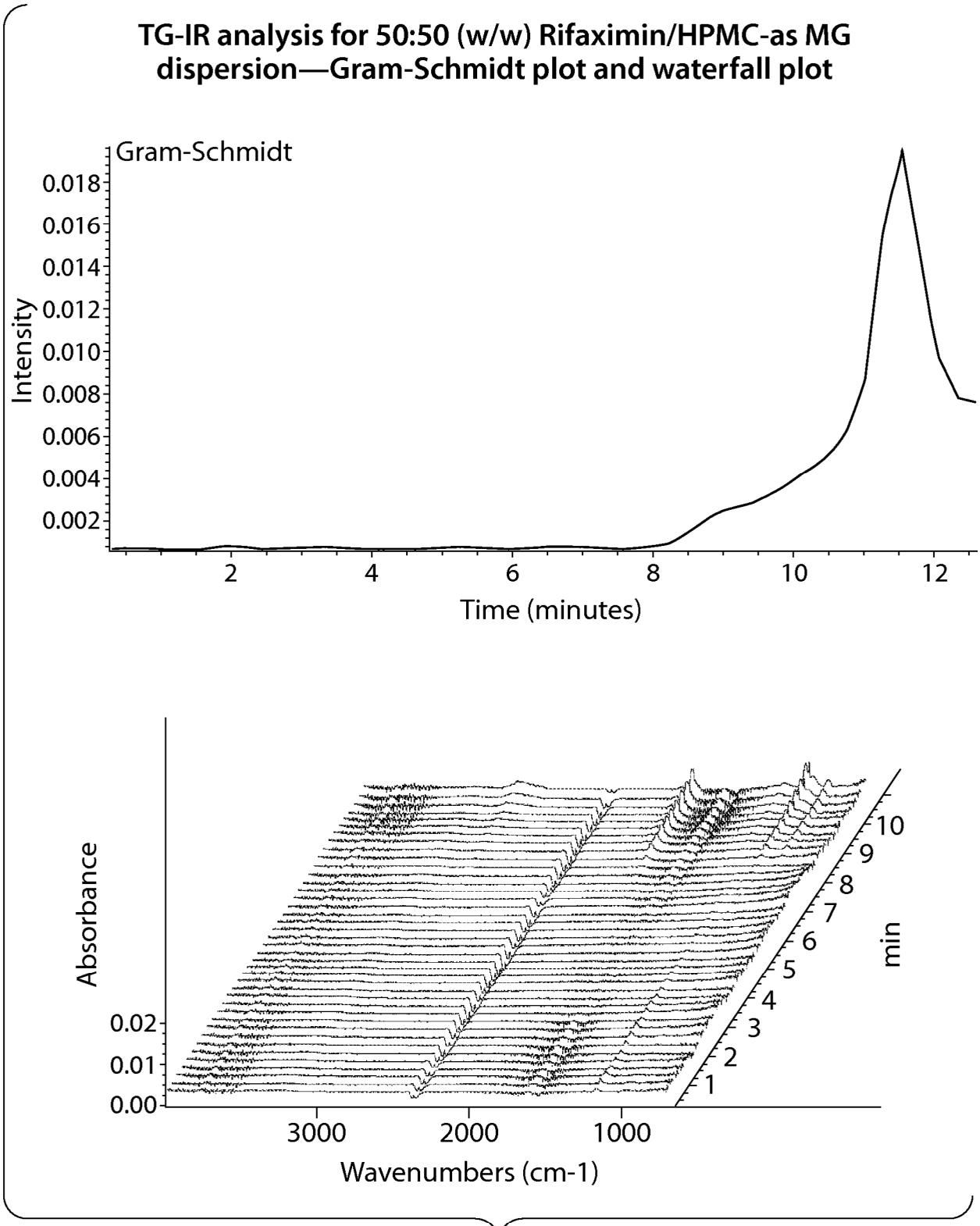

TG-IR analysis for 50:50 (w/w) Rifaximin/HPMC-as MG dispersion—Gram-Schmidt plot and waterfall plot
Gram-Schmidt
Intensity
0.018
0.016
0.014
0.012
0.010
0.008
0.006
0.004
0.002
2
4
6
8
10
12
Time (minutes)
Absorbance
0.02
0.01
0.00
3000
2000
1000
Wavenumbers (cm-1)
1
2
3
4
5
6
7
8
9
10
min

Fig. 34

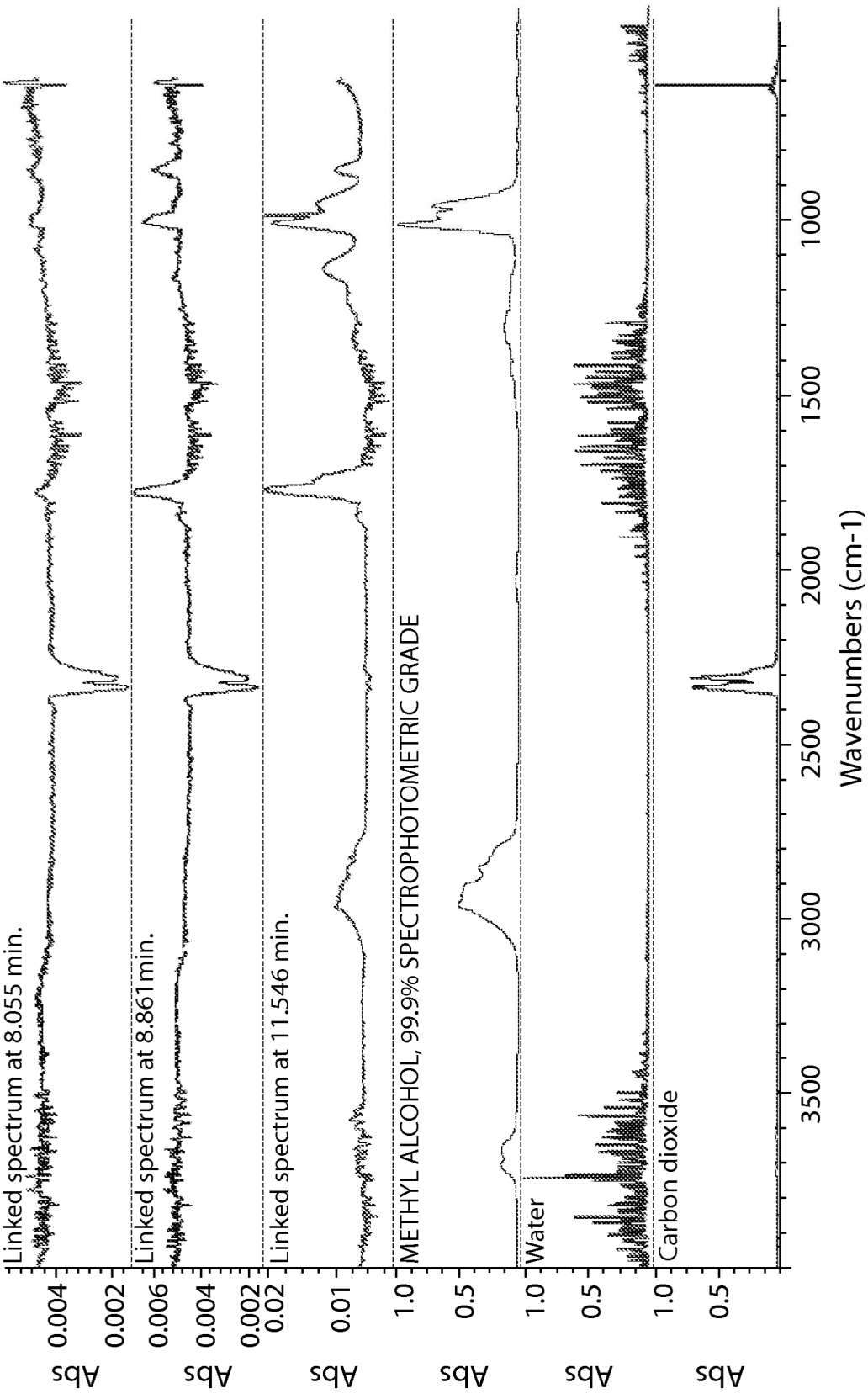

TG-IR analysis for 50:50 (w/w) Rifaximin/HPMC-AS MG dispersion
Linked spectrum at 8.055 min.
Linked spectrum at 8.861min.
Linked spectrum at 11.546 min.
METHYL ALCOHOL, 99.9% SPECTROPHOTOMETRIC GRADE
Water
Carbon dioxide
Abs
0.004
0.002
0.006
0.004
0.002
0.02
0.01
1.0
0.5
1.0
0.5
1.0
0.5
3500
3000
2500
2000
1500
1000
Wavenumbers (cm-1)

Fig. 35

XRPD pattern for 25:75 (w/w) Rifaximin/HPMC-P dispersion

top: 25:75 (w/w) Rifaximin/HPMC-P
bottom: Crystalline Rifaximin as-received

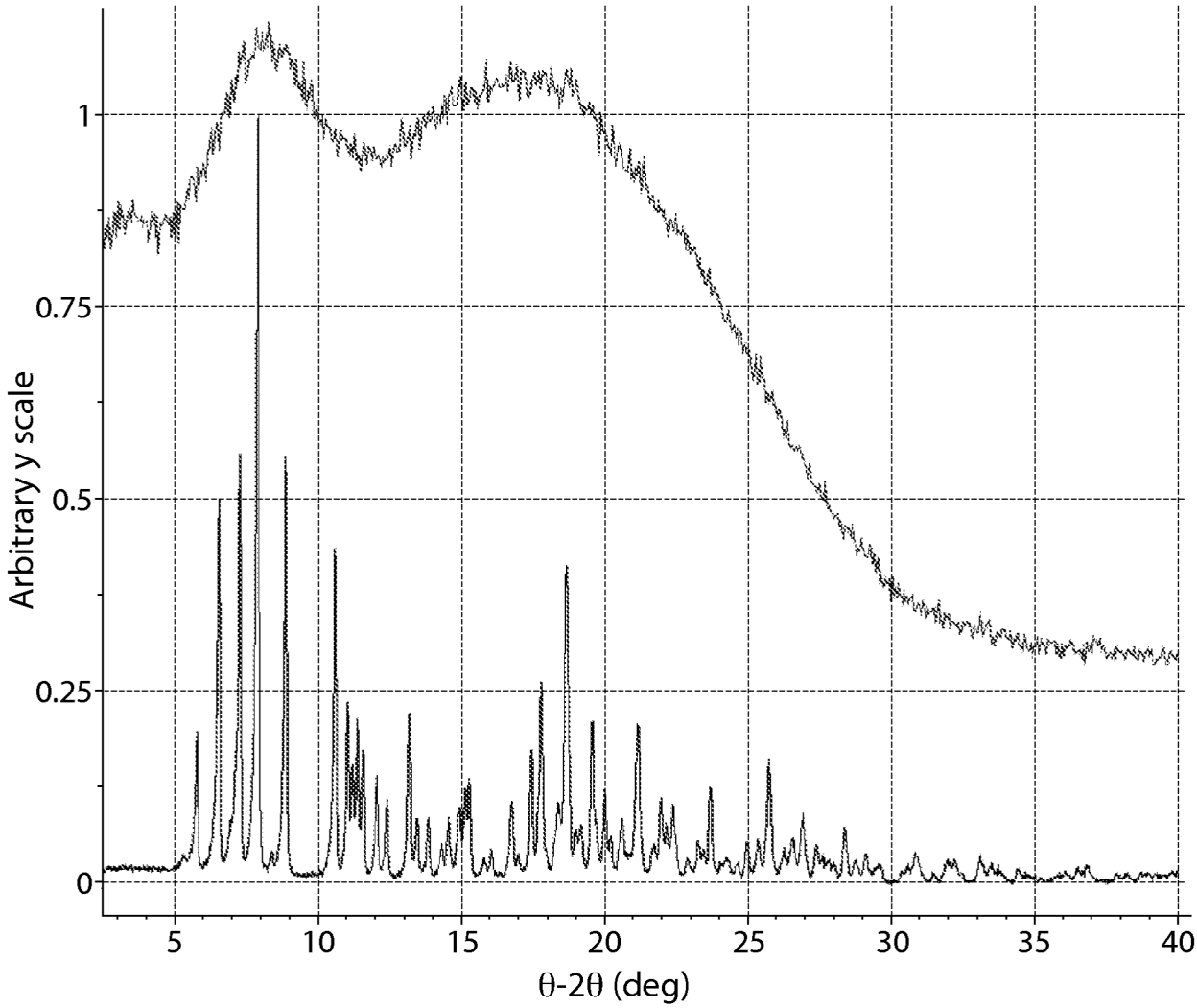


Fig. 36

Modulate DSC thermograms for 25:75 (w/w) Rifaximin/HPMC-P dispersion

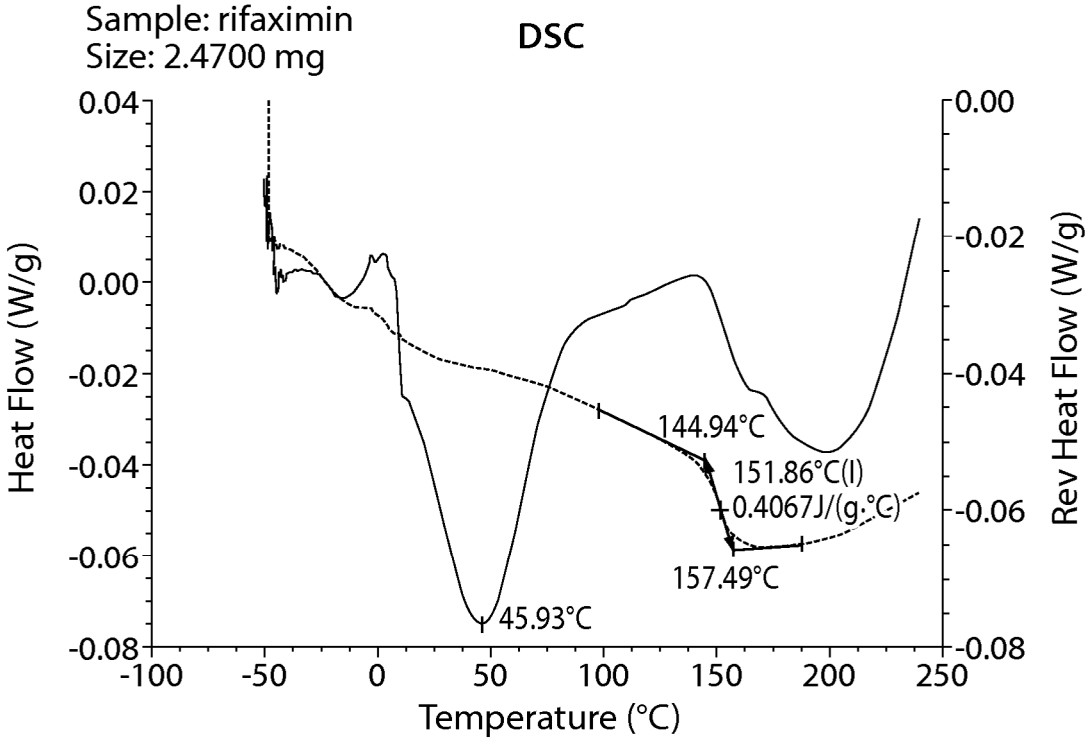


Fig. 37

TG-IR analysis for 25:75 Rifaximin/HPMC-P dispersion — TGA data

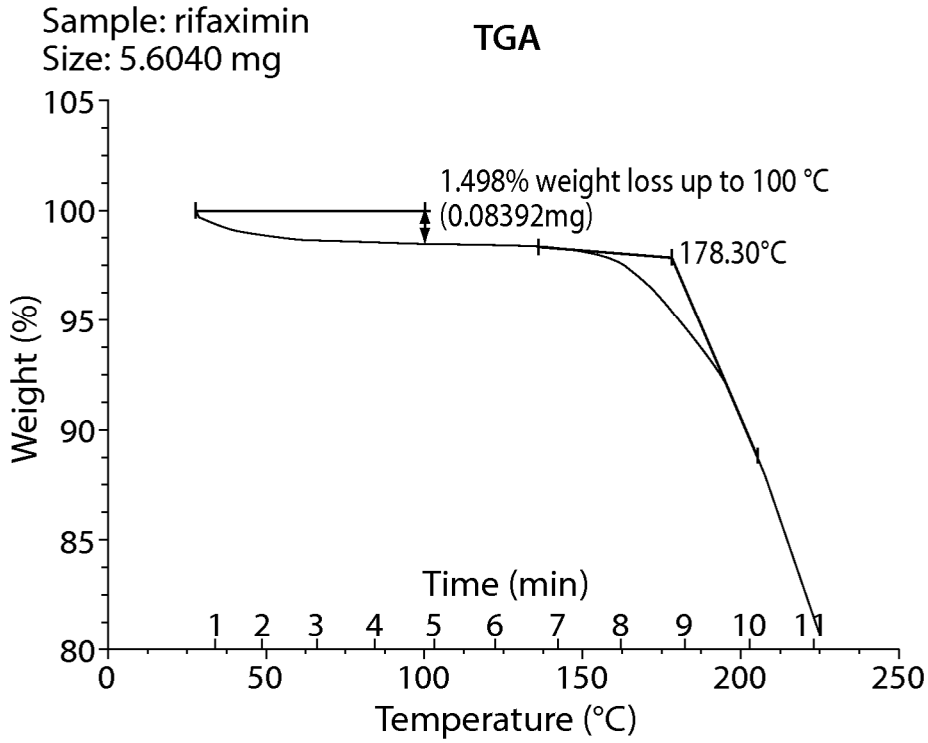


Fig. 38

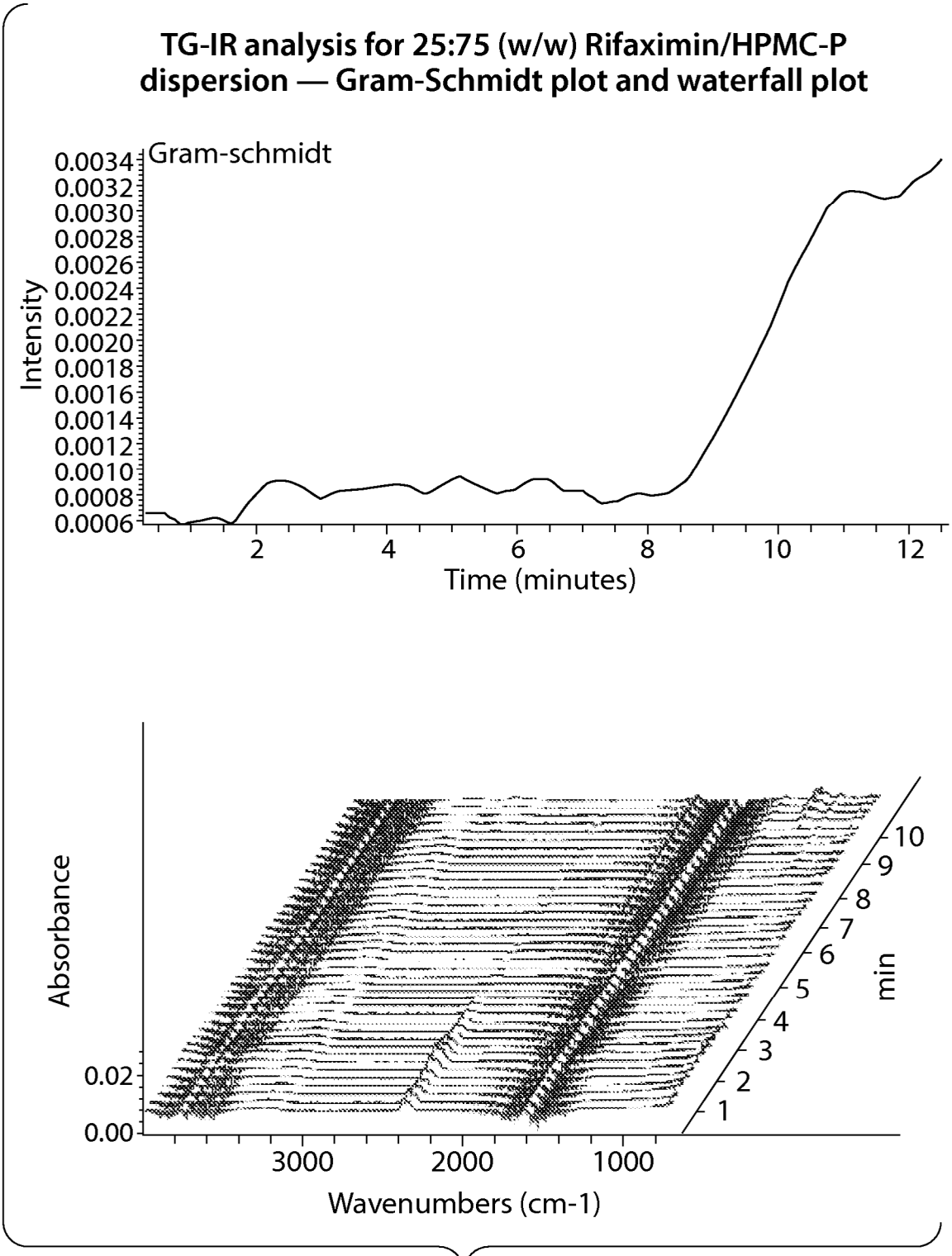

TG-IR analysis for 25:75 (w/w) Rifaximin/HPMC-P dispersion — Gram-Schmidt plot and waterfall plot
Gram-schmidt
Intensity
0.0034
0.0032
0.0030
0.0028
0.0026
0.0024
0.0022
0.0020
0.0018
0.0016
0.0014
0.0012
0.0010
0.0008
0.0006
2
4
6
8
10
12
Time (minutes)
Absorbance
0.02
0.00
3000
2000
1000
Wavenumbers (cm-1)
min
1
2
3
4
5
6
7
8
9
10

Fig. 39

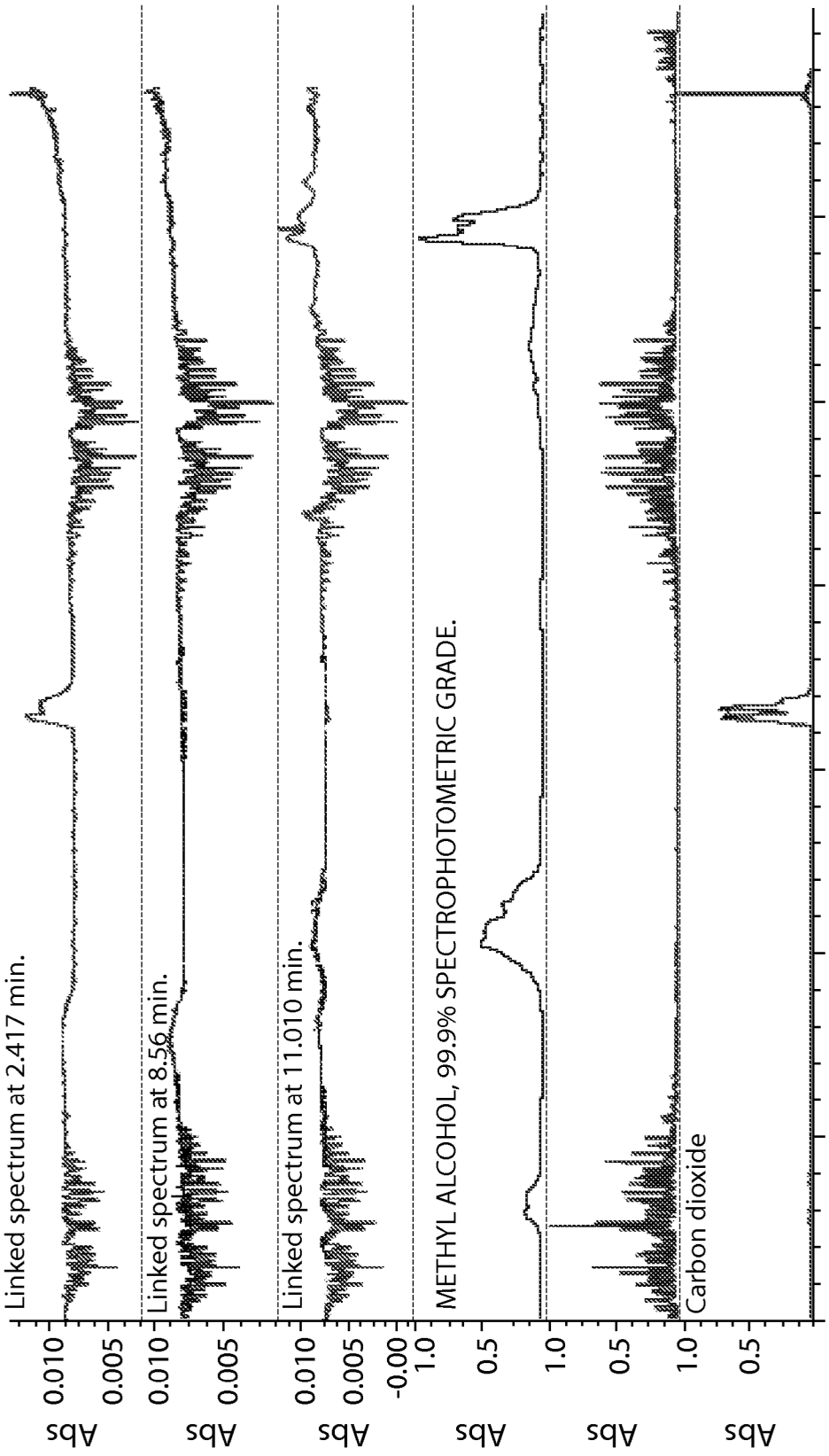

TG-IR analysis for 25:75 (w/w) Rifaximin/HPMC-P dispersion
Linked spectrum at 2.417 min.
Linked spectrum at 8.56 min.
Linked spectrum at 11.010 min.
METHYL ALCOHOL, 99.9% SPECTROPHOTOMETRIC GRADE.
Carbon dioxide
Abs
0.010
0.005
-0.00
1.0
0.5
3500
3000
2500
2000
1500
1000
Wavenumbers (cm-1)

Fig. 40

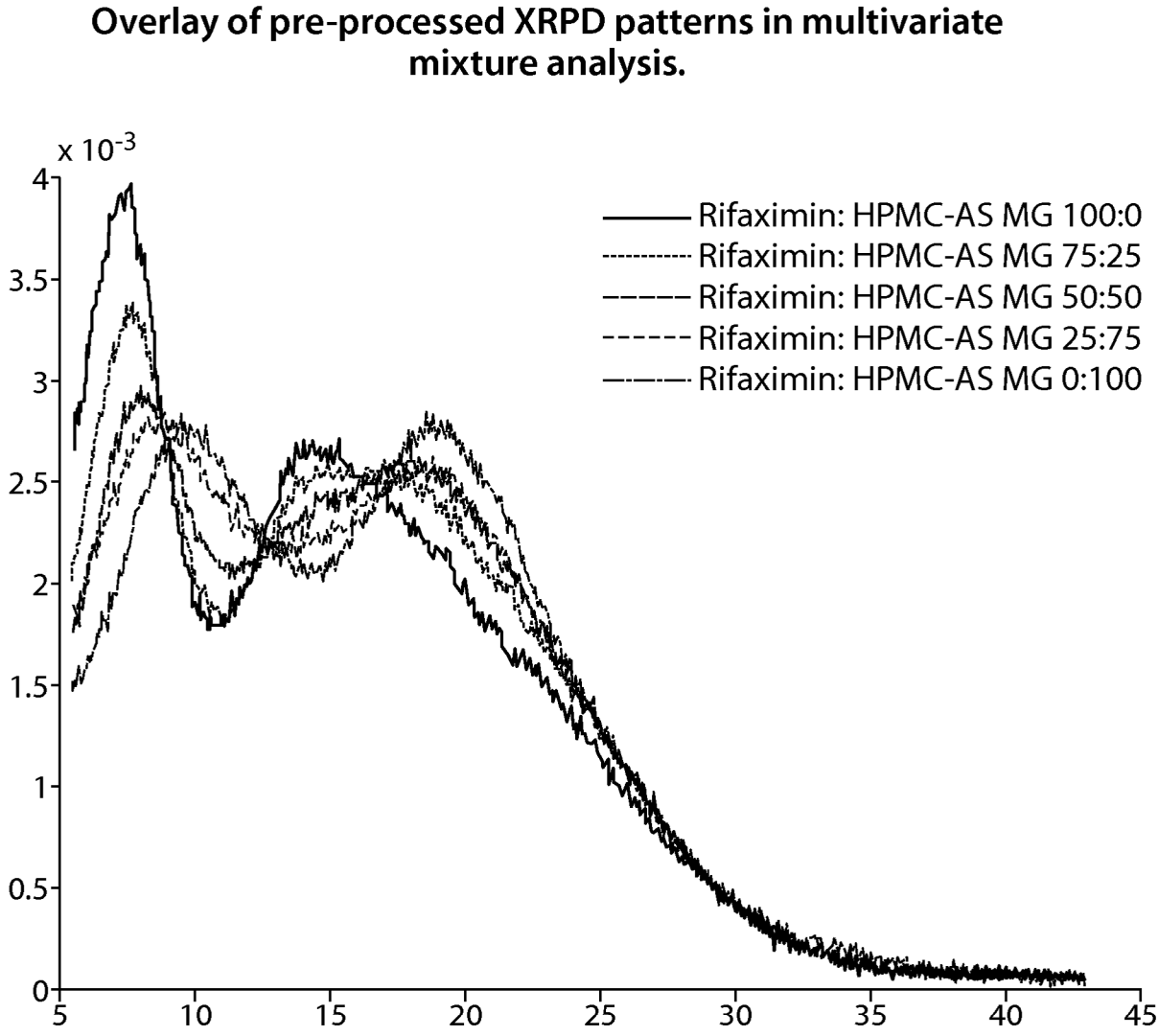

Overlay of pre-processed XRPD patterns in multivariate mixture analysis.
x 10-3
4
3.5
3
2.5
2
1.5
1
0.5
0
5
10
15
20
25
30
35
40
45
Rifaximin: HPMC-AS MG 100:0
Rifaximin: HPMC-AS MG 75:25
Rifaximin: HPMC-AS MG 50:50
Rifaximin: HPMC-AS MG 25:75
Rifaximin: HPMC-AS MG 0:100

Fig. 41

Estimated Concentrations of Rifaximin and HPMC-AS MG using Unscrambler MCR analysis.

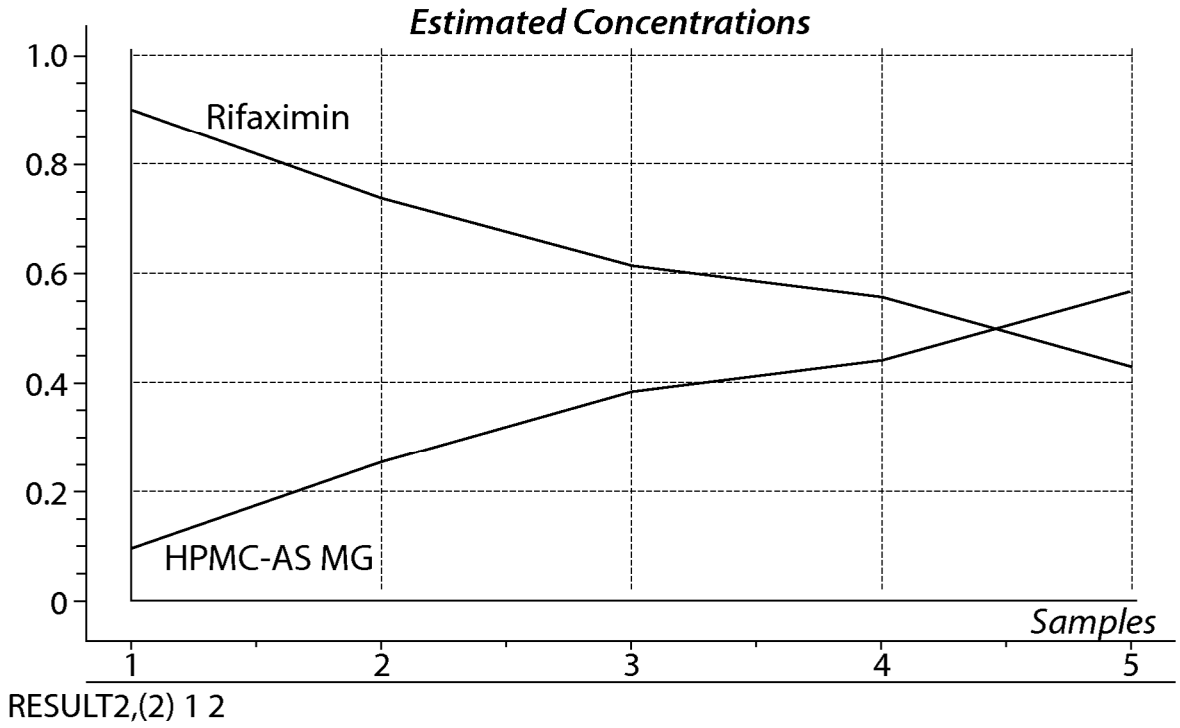


Fig. 42

Estimated XRPD patterns of Rifaximin and HPMC-AS MG using Unscrambler MCR analysis

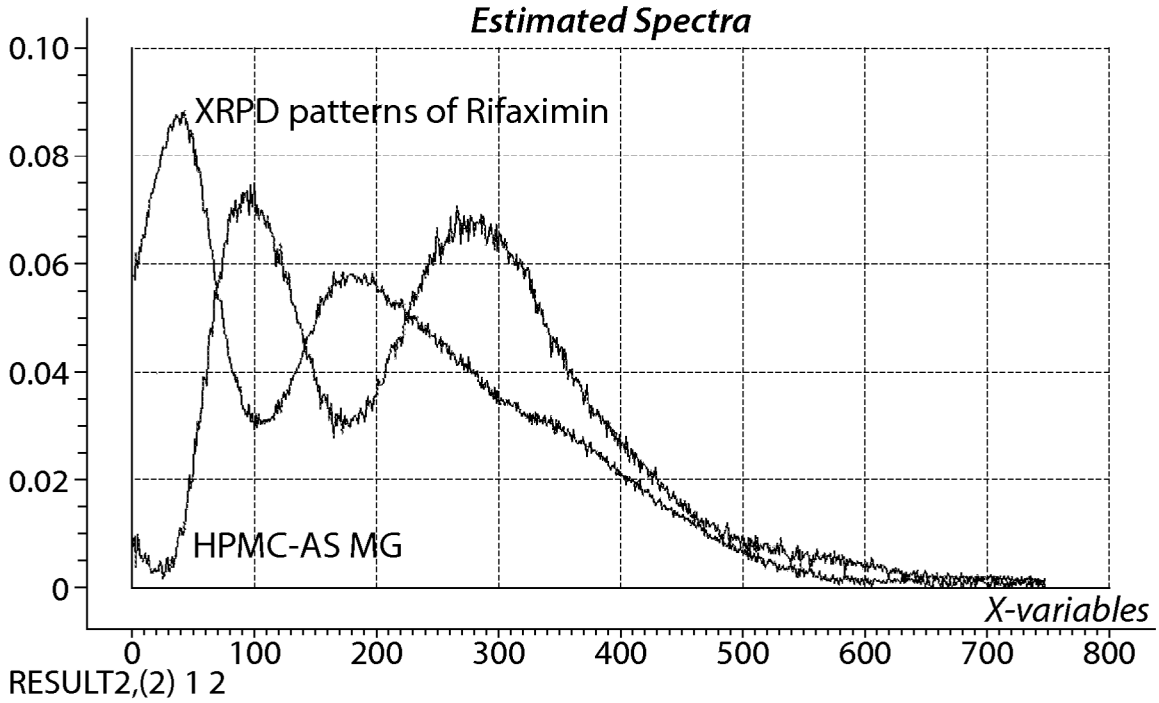


Fig. 43

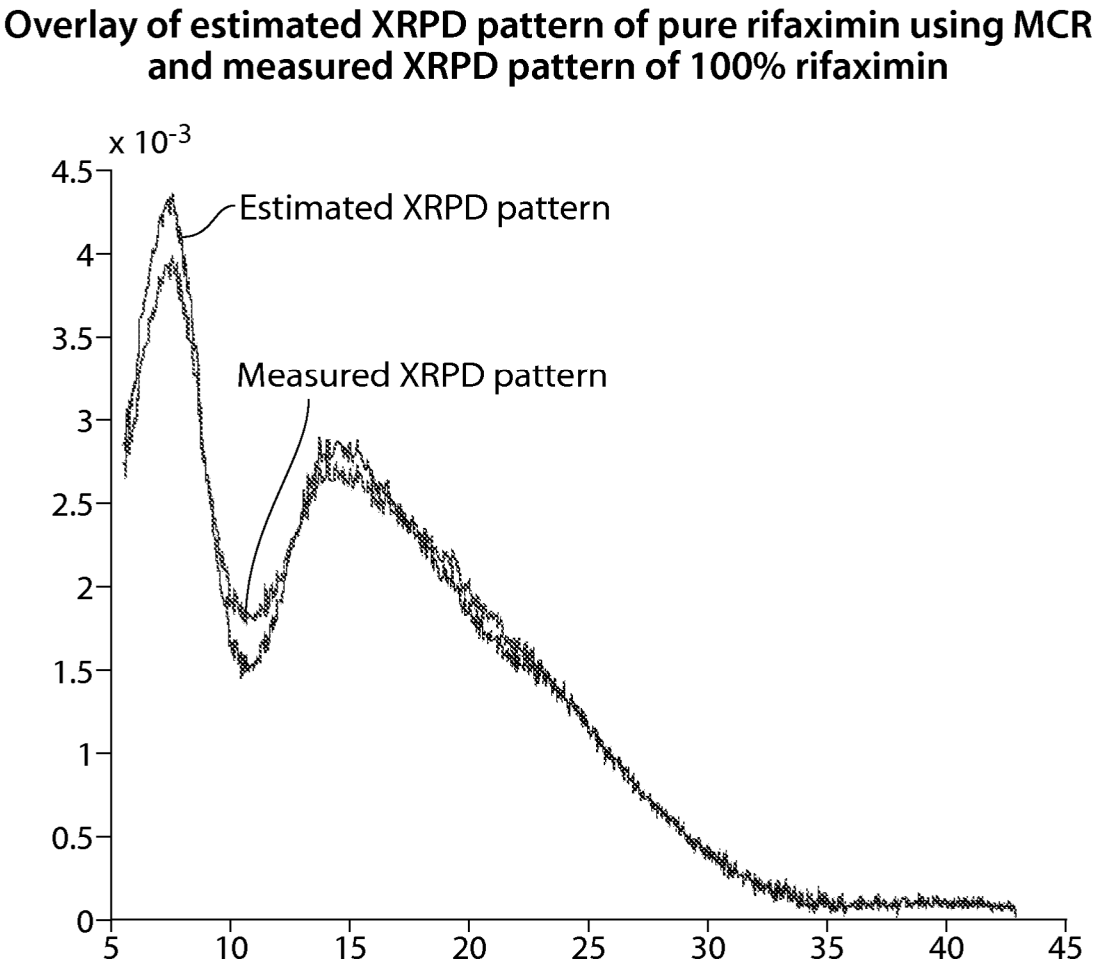

Overlay of estimated XRPD pattern of pure rifaximin using MCR and measured XRPD pattern of 100% rifaximin
x 10-3
4.5
4
3.5
3
2.5
2
1.5
1
0.5
0
Estimated XRPD pattern
Measured XRPD pattern
5
10
15
20
25
30
35
40
45

Fig. 44

Overlay of estimated XRPD pattern of pure HPMC-AS MG using MCR and measured XRPD pattern of 100% HPMC-AS MG.

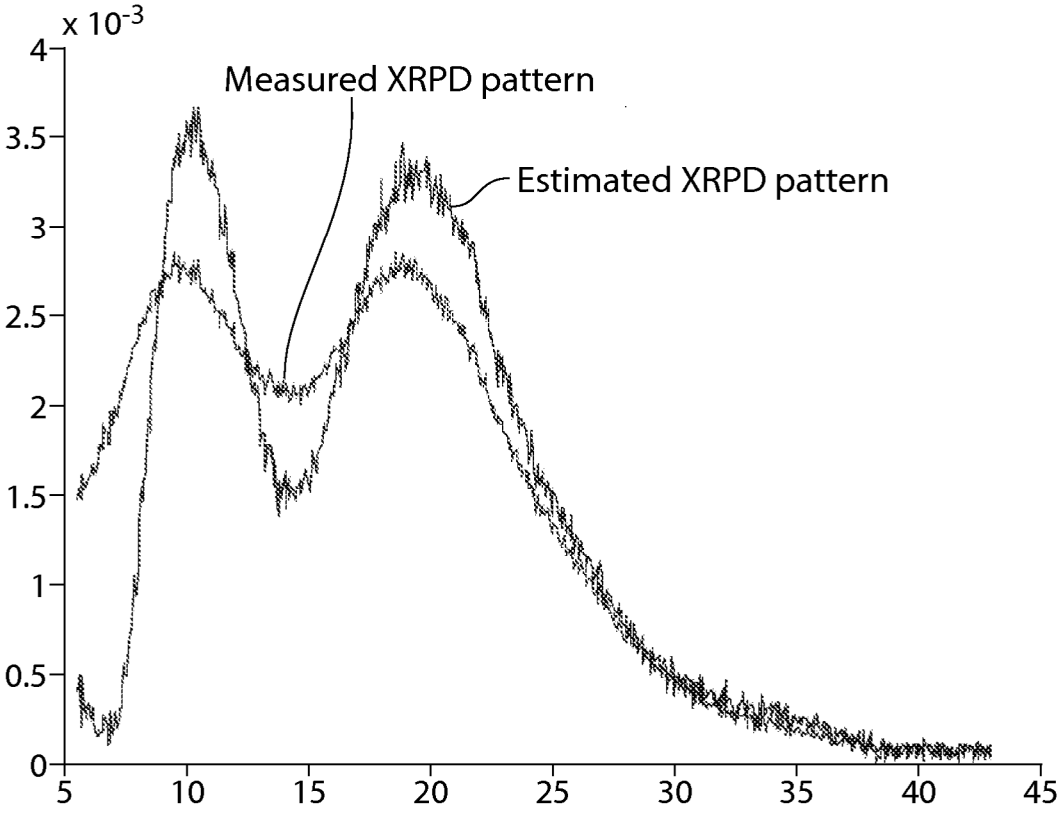


Fig. 45

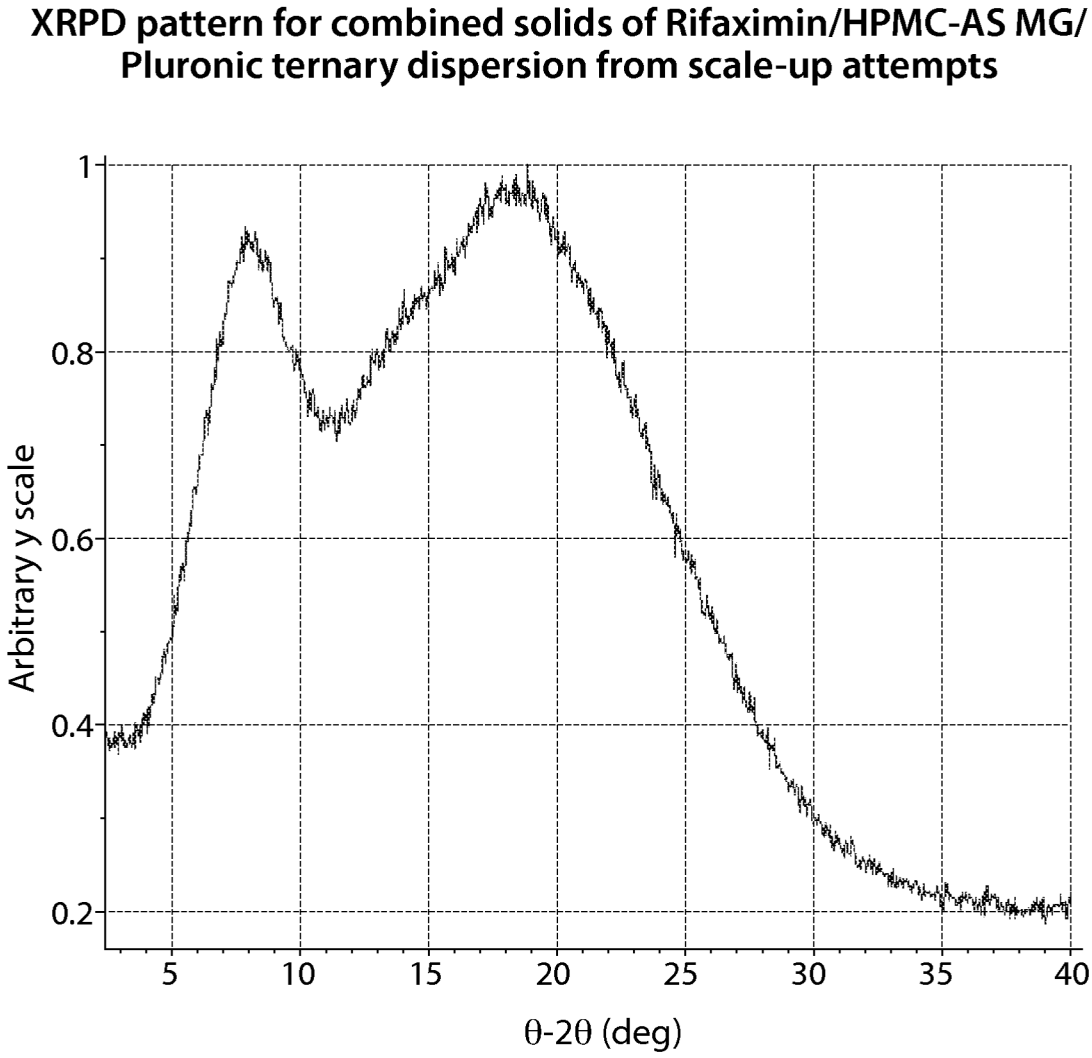

XRPD pattern for combined solids of Rifaximin/HPMC-AS MG/ Pluronic ternary dispersion from scale-up attempts
Arbitrary y scale
1
0.8
0.6
0.4
0.2
5
10
15
20
25
30
35
40
θ-2θ (deg)

Fig. 46

Modulate DSC thermogram for combined solids of Rifaximin/HPMC-AS MG/Pluronic ternary dispersion

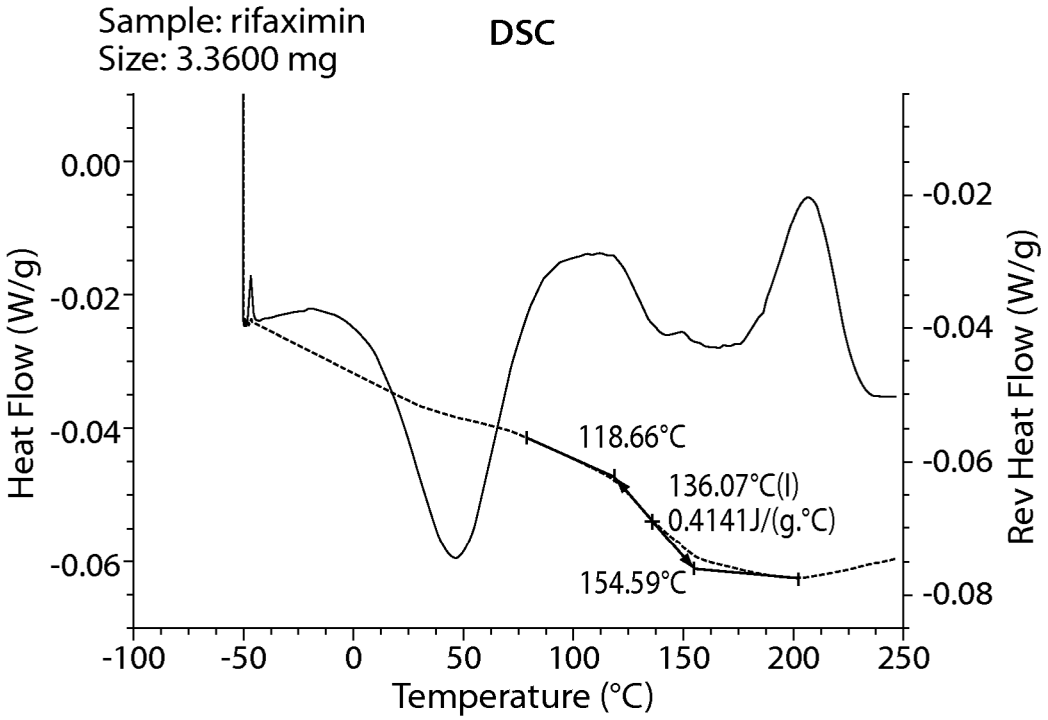


Fig. 47

TG-IR analysis for combined solids of Rifaximin/HPMC-AS MG/Pluronic ternary dispersion from scale-up attempts — TGA thermogram

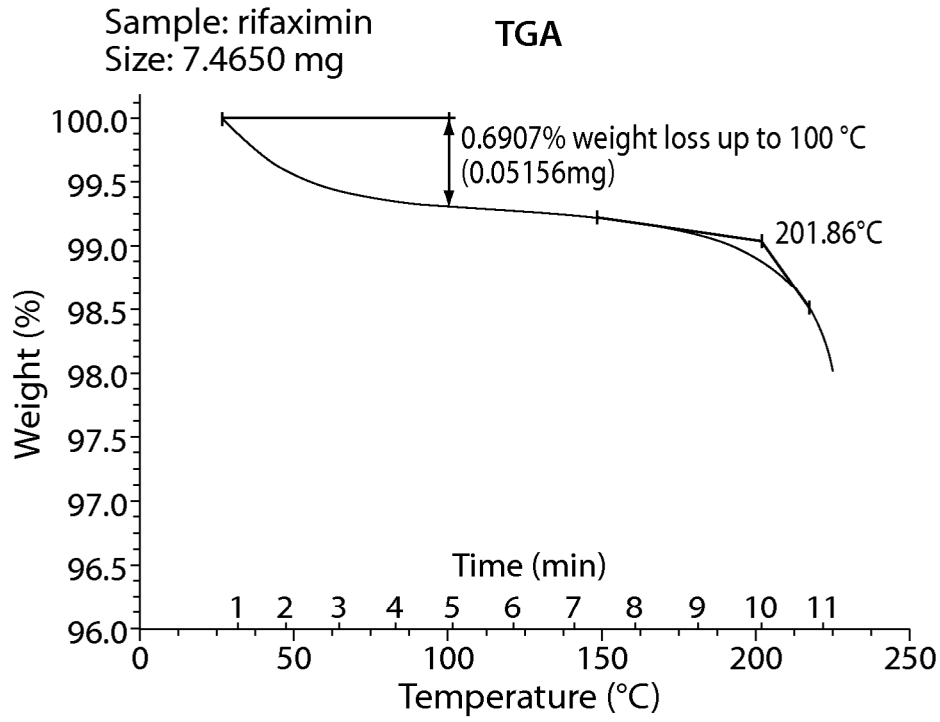


Fig. 48

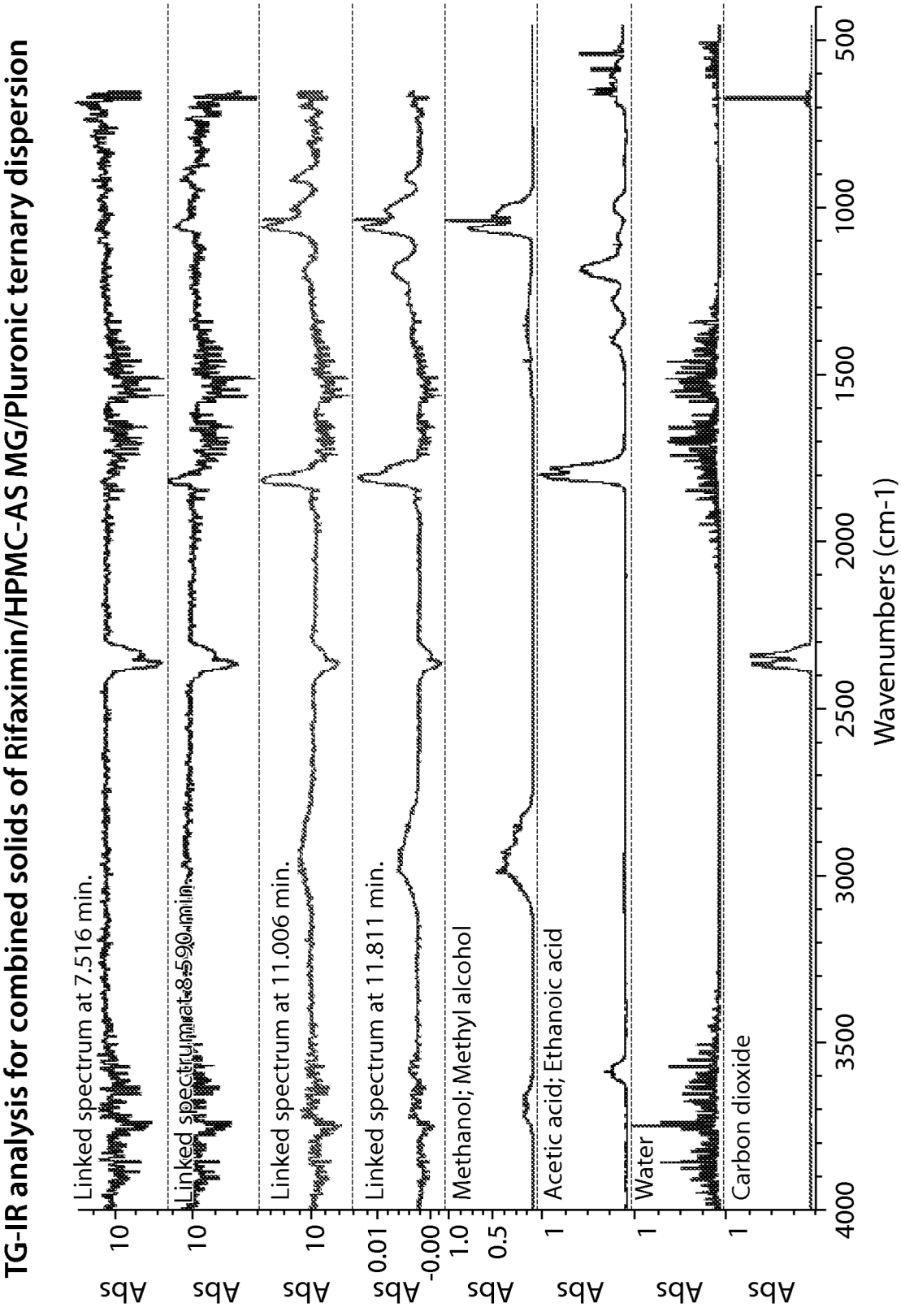

TG-IR analysis for combined solids of Rifaximin/HPMC-AS MG/Pluronic ternary dispersion
Linked spectrum at 7.516 min.
Linked spectrum at 8.590 min.
Linked spectrum at 11.006 min.
Linked spectrum at 11.811 min.
Methanol; Methyl alcohol
Acetic acid; Ethanoic acid
Water
Carbon dioxide
Abs
10
0.01
-0.00
1.0
0.5
1
4000
3500
3000
2500
2000
1500
1000
500
Wavenumbers (cm-1)

Fig. 49

Overlay of IR spectra for X-ray amorphous Rifaximin and combined solids of Rifaximin/HPMC-AS MG/Pluronic ternary dispersion.

top: X-ray amorphous Rifaximin
bottom: Rifaximin/HPMC-AS MG/Pluronic ternary dispersion

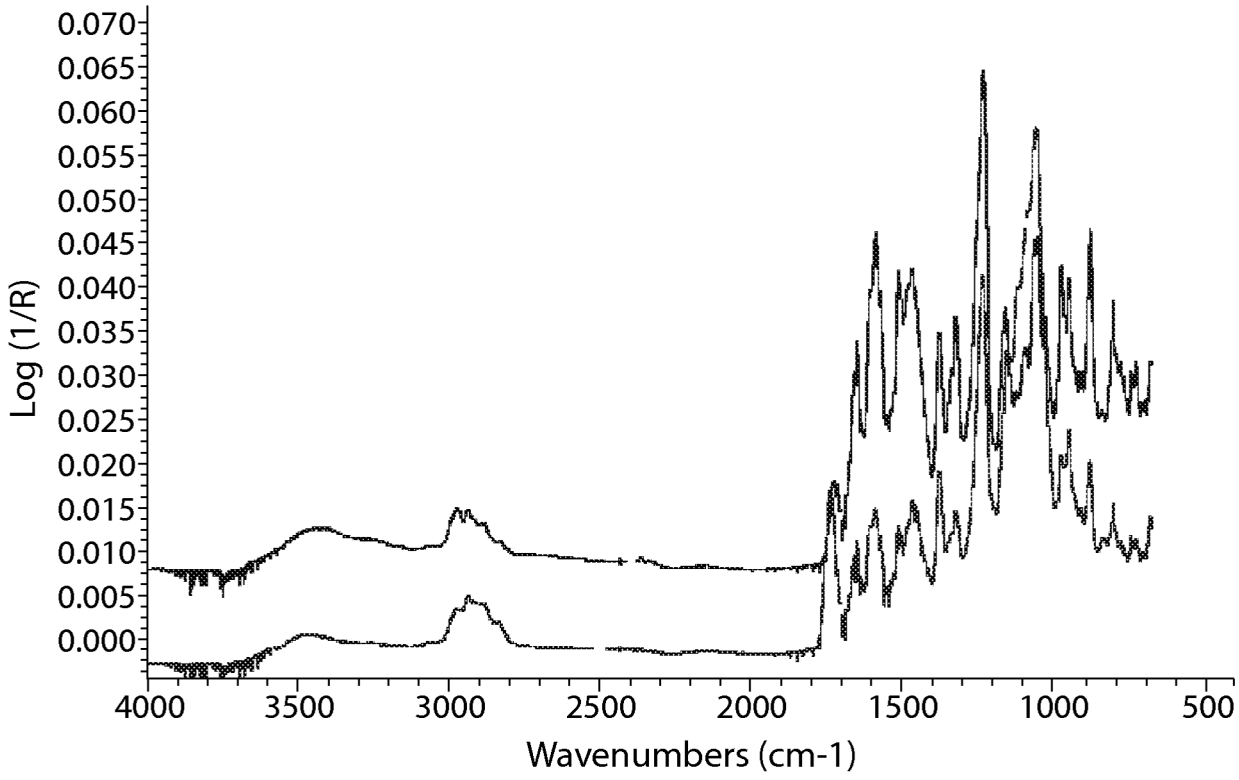


Fig. 50

Overlay of Ramam spectra for X-ray amorphous Rifaximin and combined solids of Rifaximin/HPMC-AS MG/Pluronic ternary dispersion.

top: X-ray amorphous Rifaximin
bottom: Rifaximin/HPMC-AS MG/Pluronic ternary dispersion

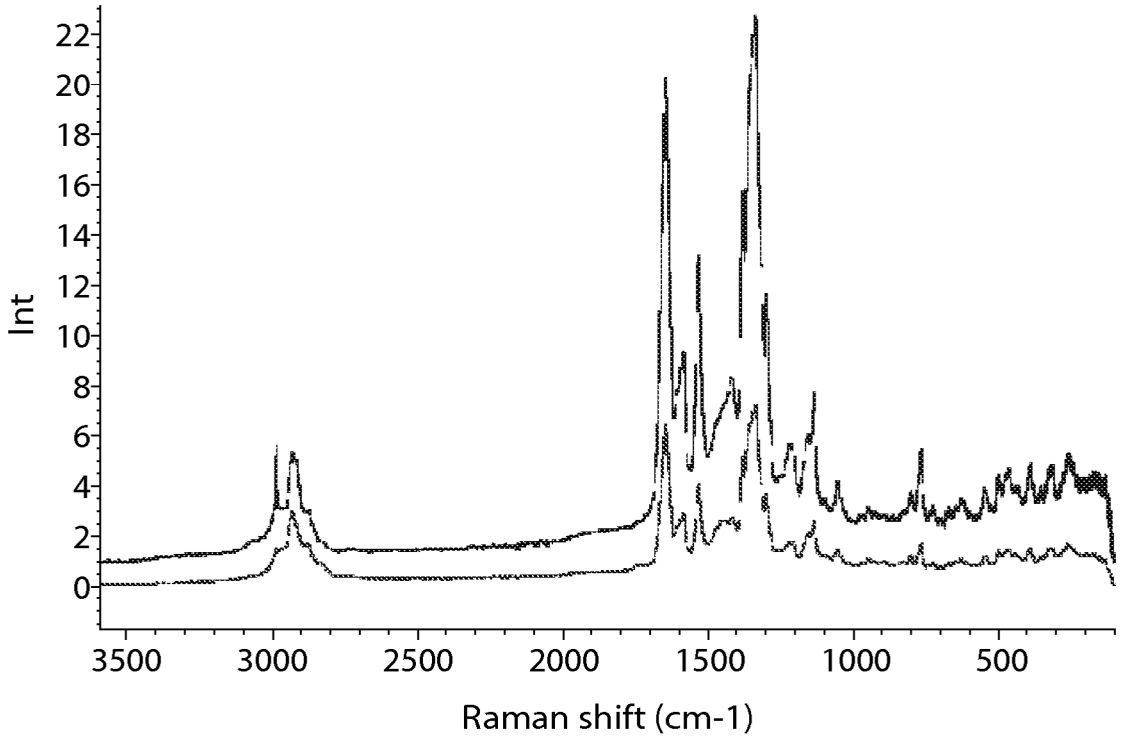


Fig. 51

Particle size analysis report for combined solids of Rifaximin/HPMC-AS MG/Pluronic ternary dispersion from scale-up attempts

Particle Name: Rifaximin SDD	**Dispersant Name:** 2% (w/v) Lecithin in isopar G	**Analysis model:** General purpose	**Weighted Residual:** 0.478 %
Particle RI: 1.560	**Dispersant RI:** 1.420	**Sensitivity:** Normal	**Obscuration:** 12.32 %
Absorption: 0.01	**Size range:** 0.020 to 2000.000 µm	**Irregular Shape Mode:** On	**Result units:** Volume
Stirrer Speed: 0 rpm	**Pump Speed:** 1600 rpm	**Disperser Pressure:** 0 bar	**Feed Rate:** 0 %

Vol. Weighted Mean D[4,3]: 10.910 µm

d(0.95): 21.598 µm

d(0.1): 3.627 µm **d(0.5):** 8.233 µm **d(0.9):** 17.530 µm

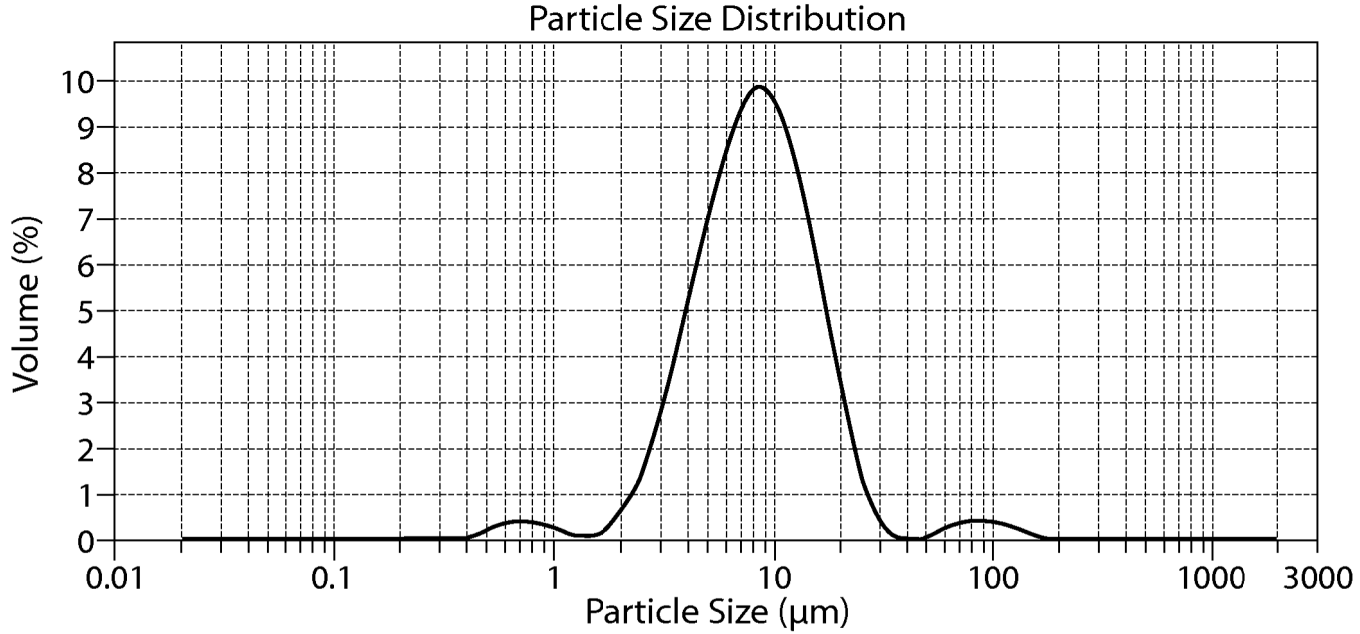


Fig. 52

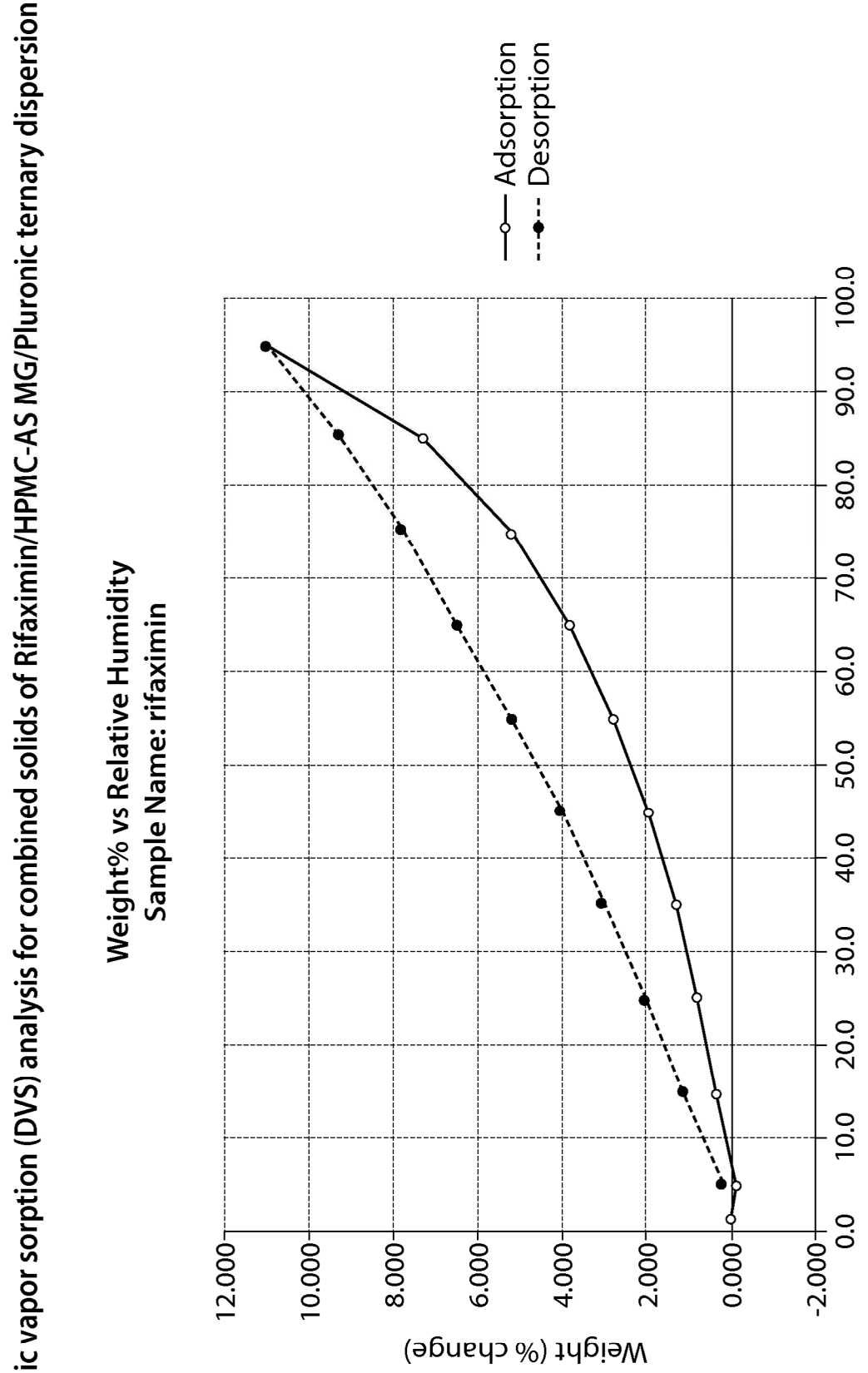

Dynamic vapor sorption (DVS) analysis for combined solids of Rifaximin/HPMC-AS MG/Pluronic ternary dispersion
Weight% vs Relative Humidity
Sample Name: rifaximin
Adsorption
Desorption
Weight (% change)
12.000
10.000
8.000
6.000
4.000
2.000
0.000
-2.000
0.0
10.0
20.0
30.0
40.0
50.0
60.0
70.0
80.0
90.0
100.0
%RH

Fig. 53

Overlay of XRPD patterns for Rifaximin/HPMC-AS MG/Pluronic ternary dispersion post-DVS solids and solids as-prepared

top: post-DVS solids of Rifaximin/HPMC-AS MG/Pluronic ternary dispersion
bottom: Rifaximin/HPMC-AS MG/Pluronic ternary dispersion as-prepared

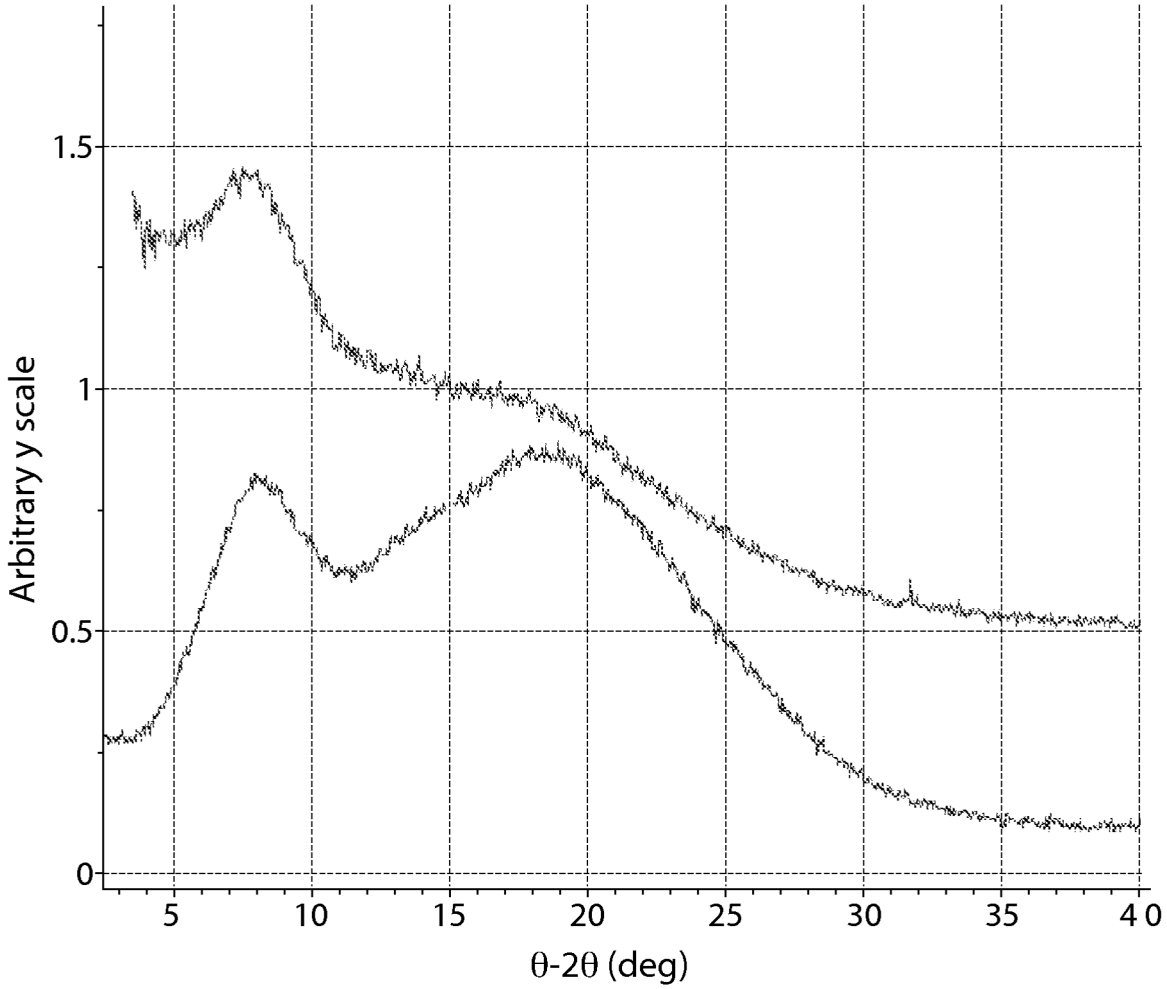


Fig. 54

Overlay of XRPD patterns for Rifaximin ternary dispersion post-stressed samples and as-prepared sample

top: Rifaximin ternary dispersion after stressed at 40 °C/75%RH for 12 weeks
second: Rifaximin ternary dispersion after stressed at 40 °C/75%RH for 6 weeks
third: Rifaximin ternary dispersion after stressed at 70 °C/75%RH for 3 weeks
fourth: Rifaximin ternary dispersion after stressed at 70 °C/75%RH for 1 week
bottom: Rifaximin ternary dispersion as-prepared

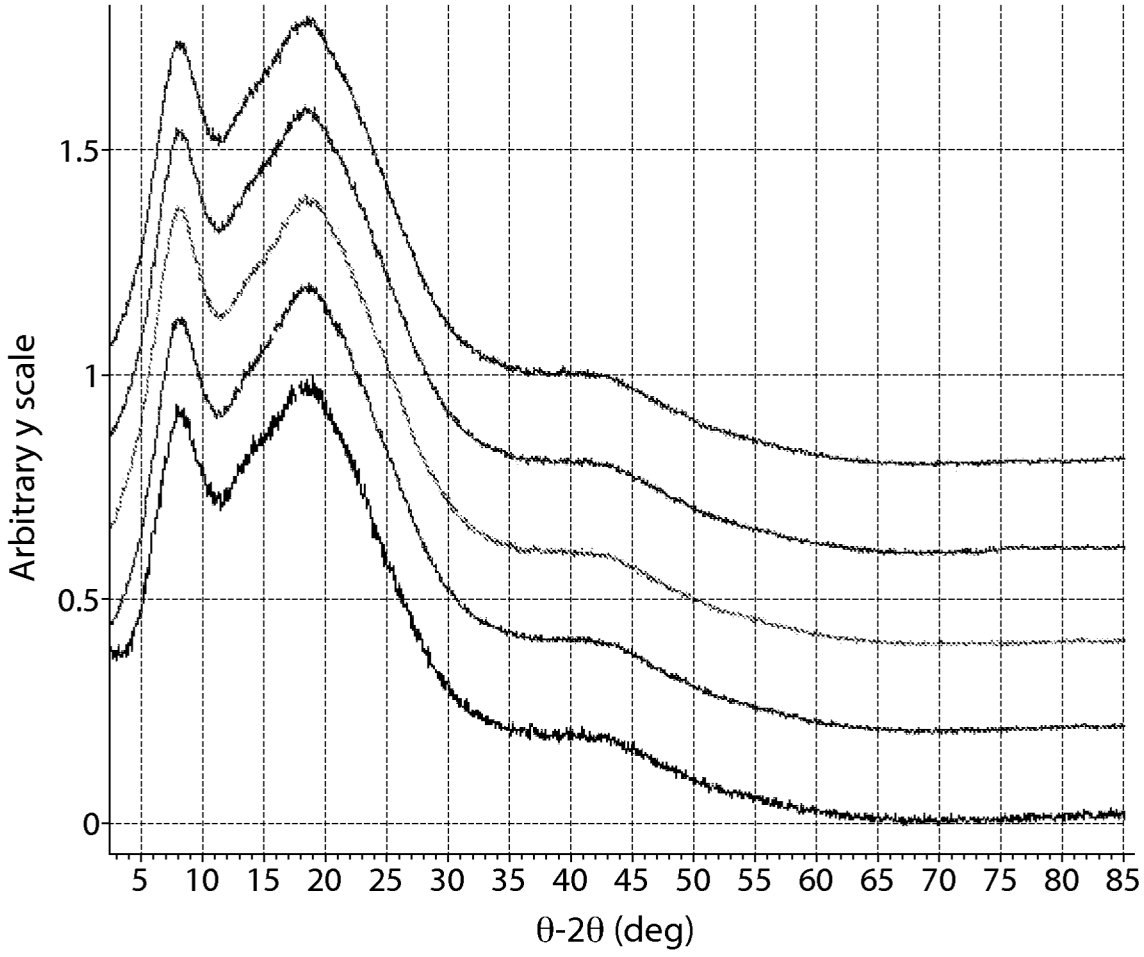


Fig. 55

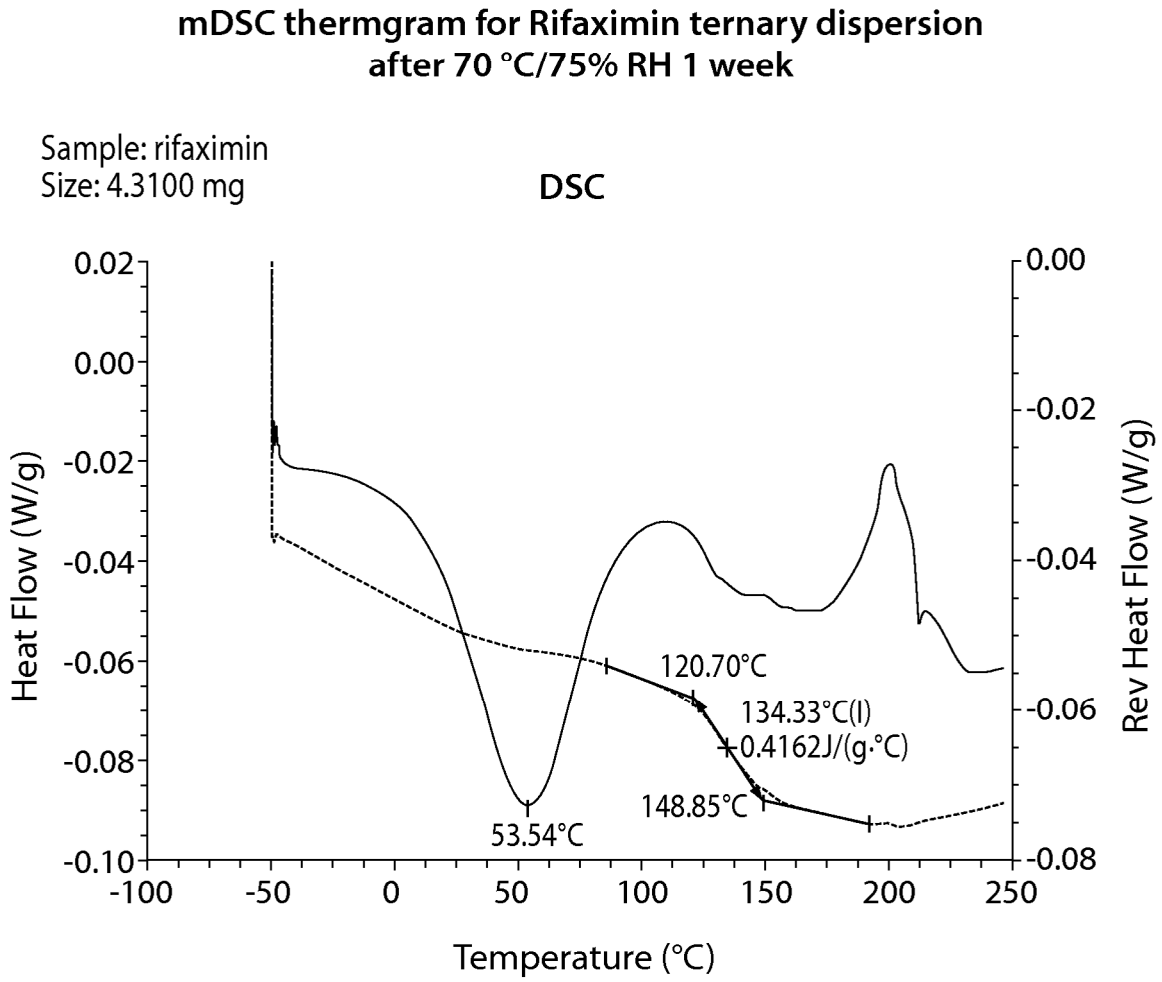

mDSC thermgram for Rifaximin ternary dispersion
after 70 °C/75% RH 1 week
Sample: rifaximin
Size: 4.3100 mg
DSC
Heat Flow (W/g)
Rev Heat Flow (W/g)
Temperature (°C)
120.70°C
134.33°C(I)
0.4162J/(g·°C)
148.85°C
53.54°C

Fig. 56

mDSC thermgram for Rifaximin ternary dispersion after 70 °C/75% RH 3 weeks

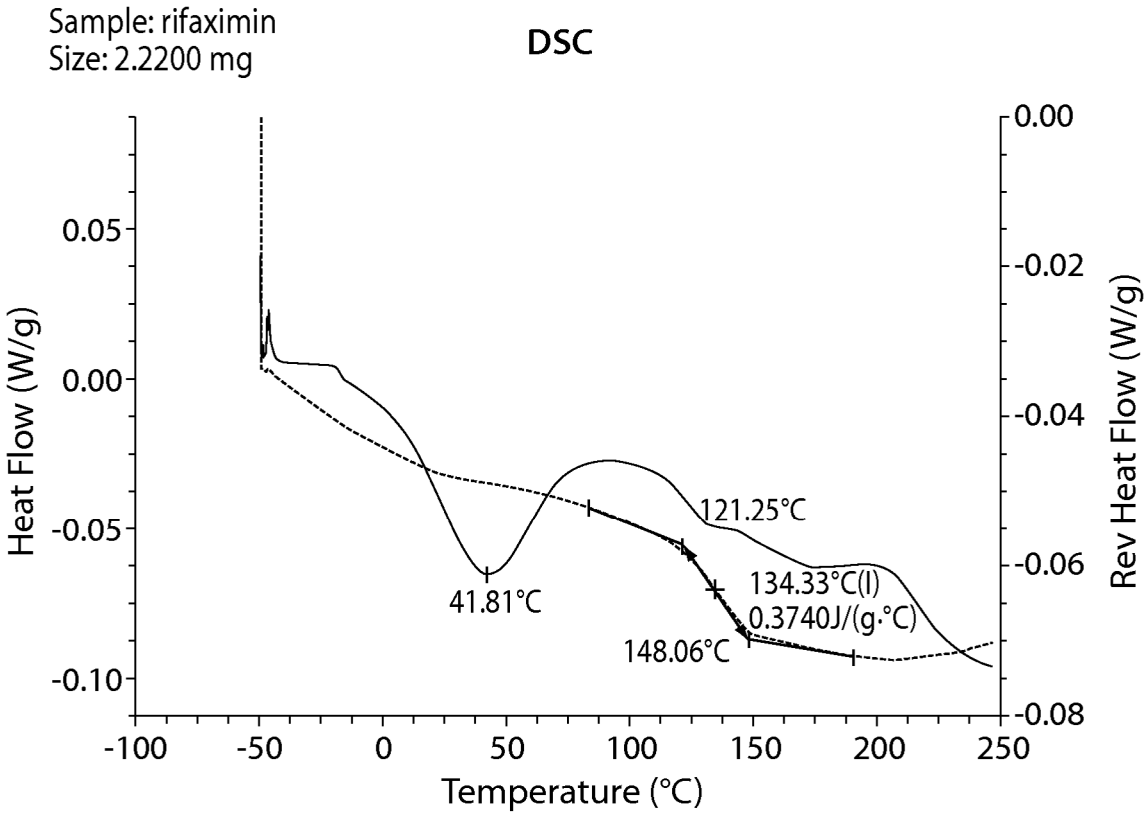


Fig. 57

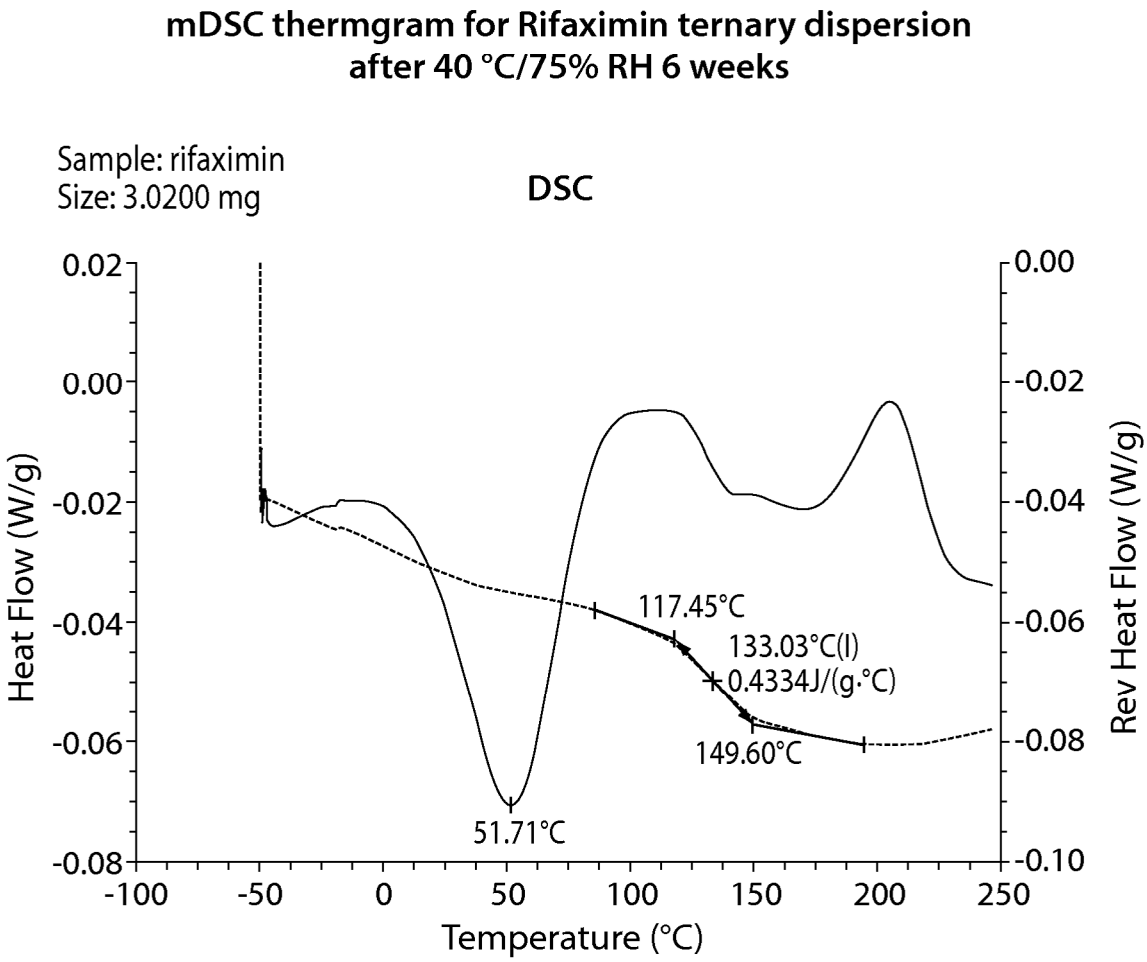

mDSC thermgram for Rifaximin ternary dispersion
after 40 °C/75% RH 6 weeks
Sample: rifaximin
Size: 3.0200 mg
DSC
Heat Flow (W/g)
Rev Heat Flow (W/g)
Temperature (°C)
0.02
0.00
-0.02
-0.04
-0.06
-0.08
-0.10
-100
-50
0
50
100
150
200
250
117.45°C
133.03°C(l)
0.4334J/(g·°C)
149.60°C
51.71°C

Fig. 58

mDSC thermgram for Rifaximin ternary dispersion after 40 °C/75% RH 12 weeks

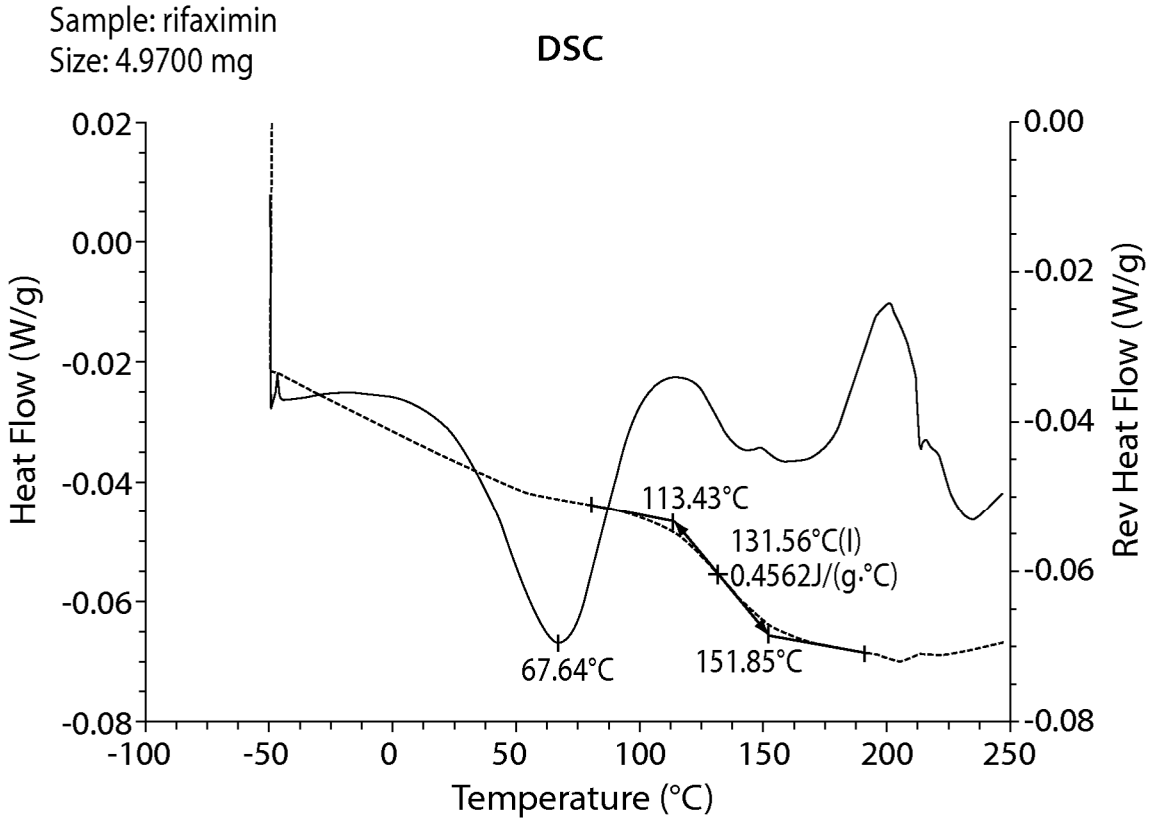


Fig. 59

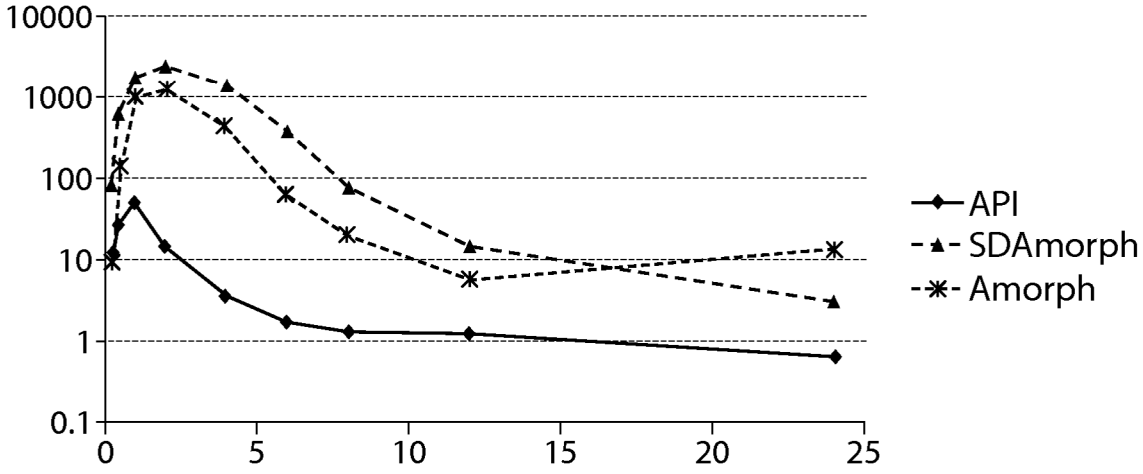

10000
1000
100
10
1
0.1
0
5
10
15
20
25
API
SDAmorph
Amorph

Fig. 60

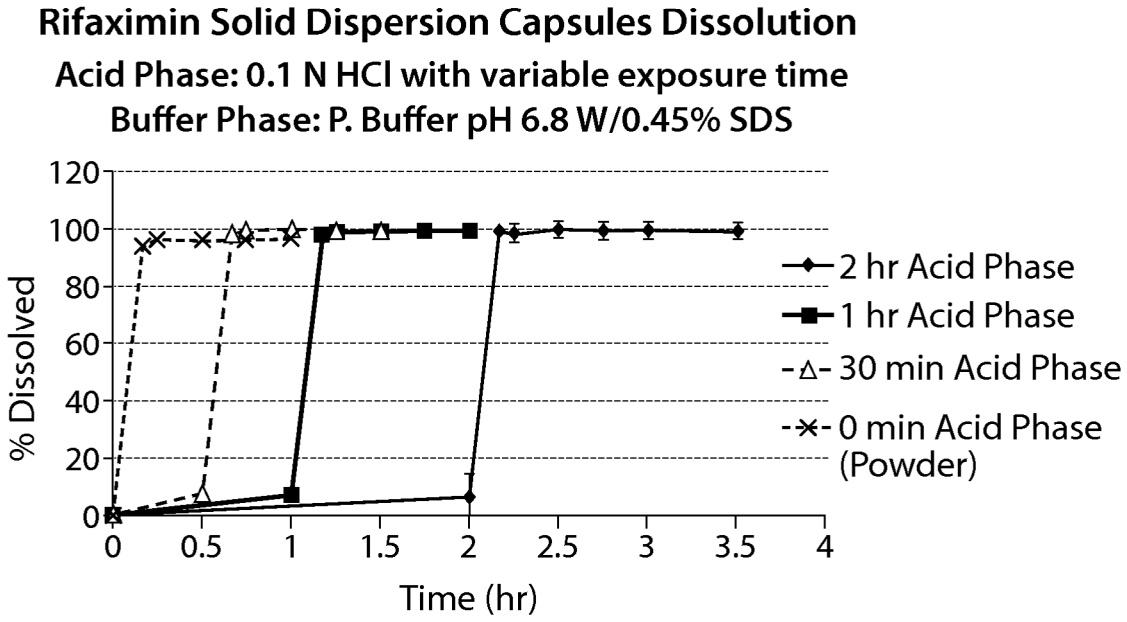

Rifaximin Solid Dispersion Capsules Dissolution
Acid Phase: 0.1 N HCl with variable exposure time
Buffer Phase: P. Buffer pH 6.8 W/0.45% SDS
% Dissolved
120
100
80
60
40
20
0
0
0.5
1
1.5
2
2.5
3
3.5
4
Time (hr)
2 hr Acid Phase
1 hr Acid Phase
30 min Acid Phase
0 min Acid Phase (Powder)

Fig. 61

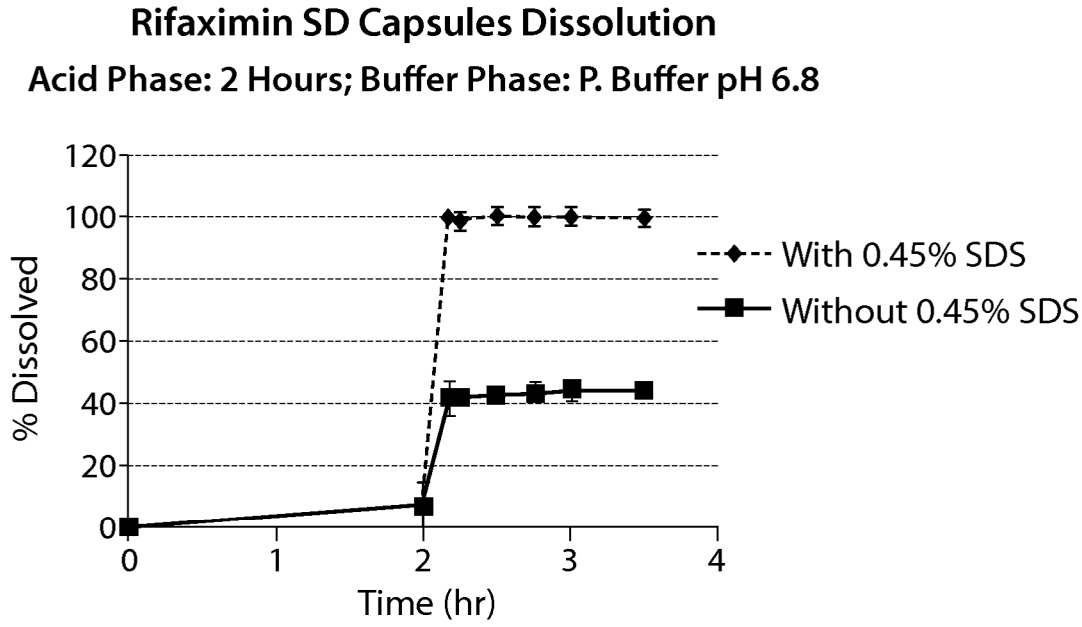

Rifaximin SD Capsules Dissolution
Acid Phase: 2 Hours; Buffer Phase: P. Buffer pH 6.8
% Dissolved
120
100
80
60
40
20
0
0
1
2
3
4
Time (hr)
With 0.45% SDS
Without 0.45% SDS

Fig. 62

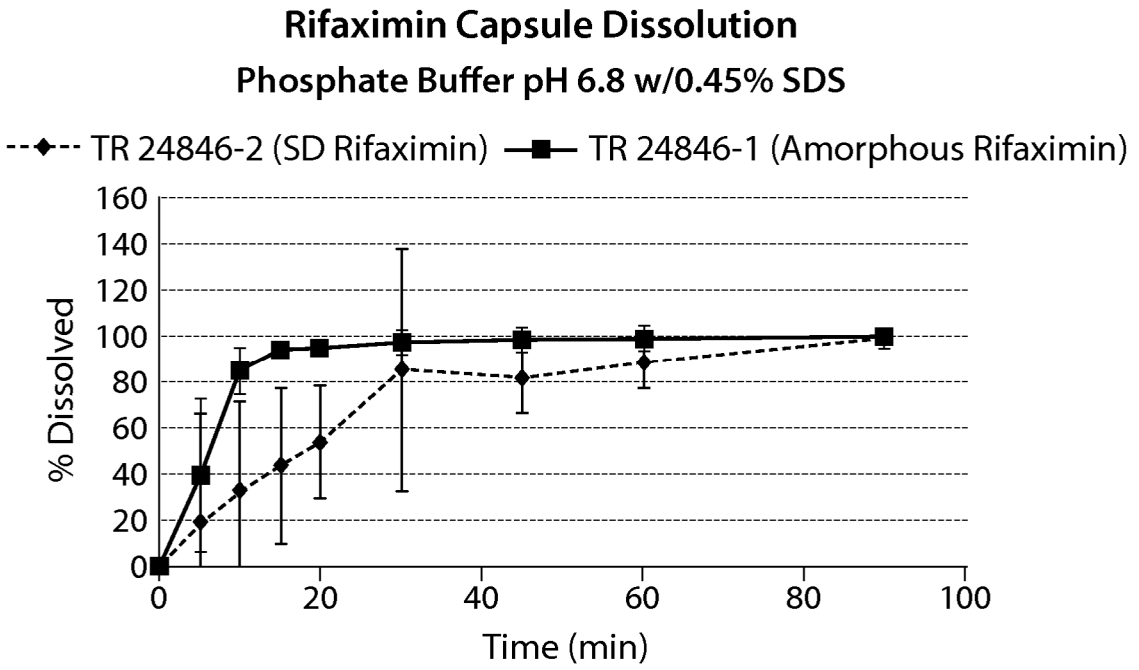

Rifaximin Capsule Dissolution
Phosphate Buffer pH 6.8 w/0.45% SDS
TR 24846-2 (SD Rifaximin)
TR 24846-1 (Amorphous Rifaximin)
% Dissolved
160
140
120
100
80
60
40
20
0
0
20
40
60
80
100
Time (min)

Fig. 63

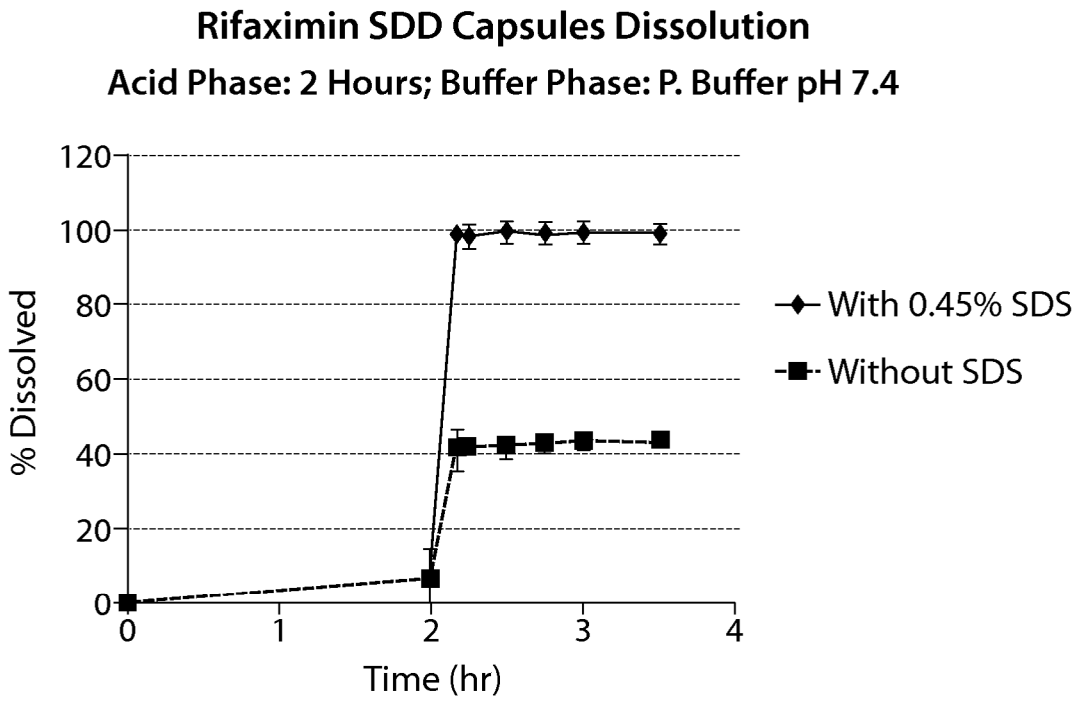


Fig. 64A

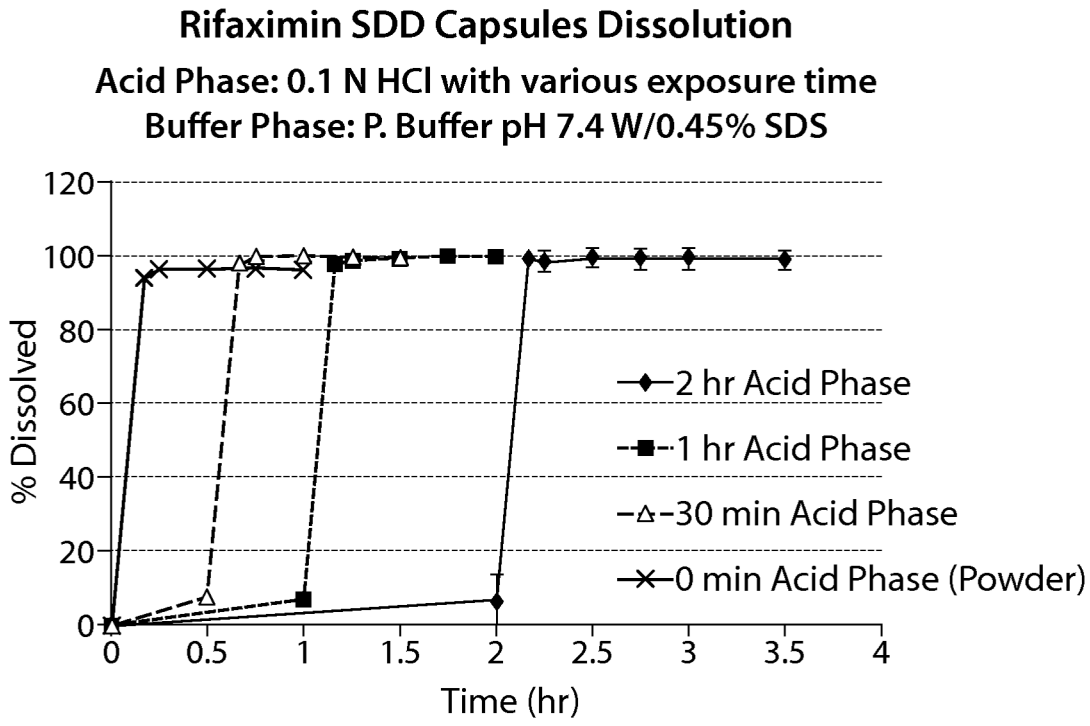
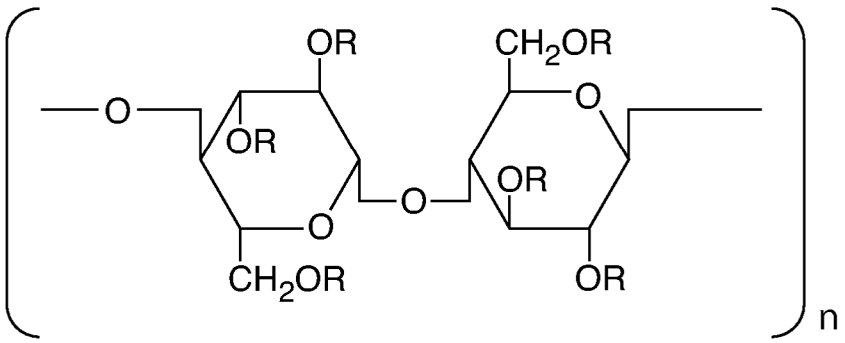


Fig. 64B



HPMC-AS

Fig. 64C

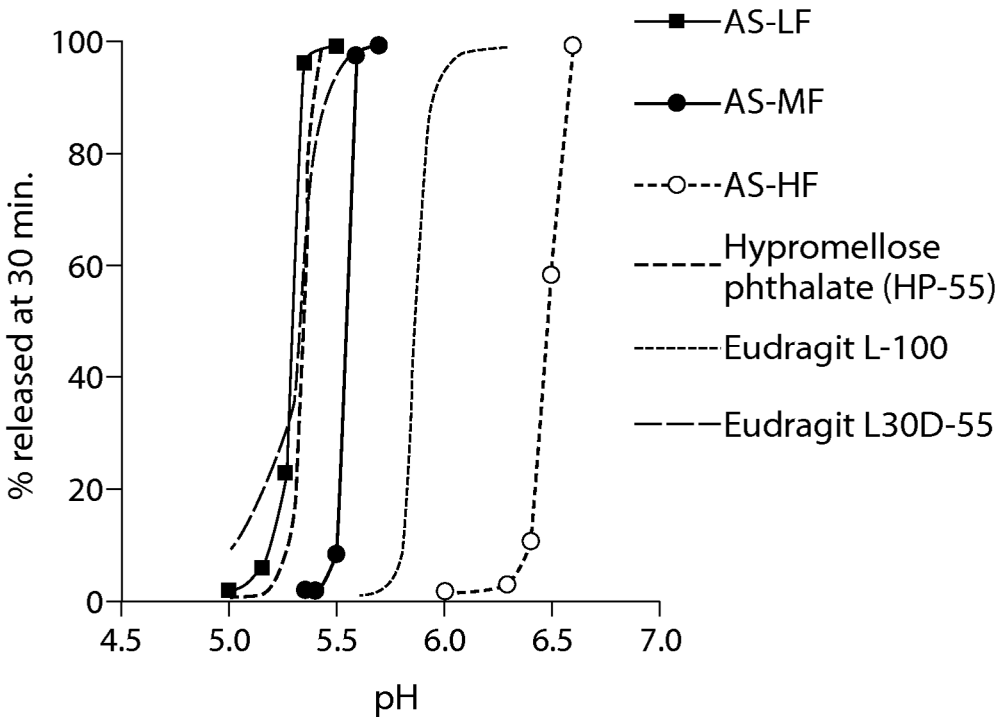


Fig. 64D

Rifaximin SDD with 10% CS Formulation was Used in Human Clinical Studies

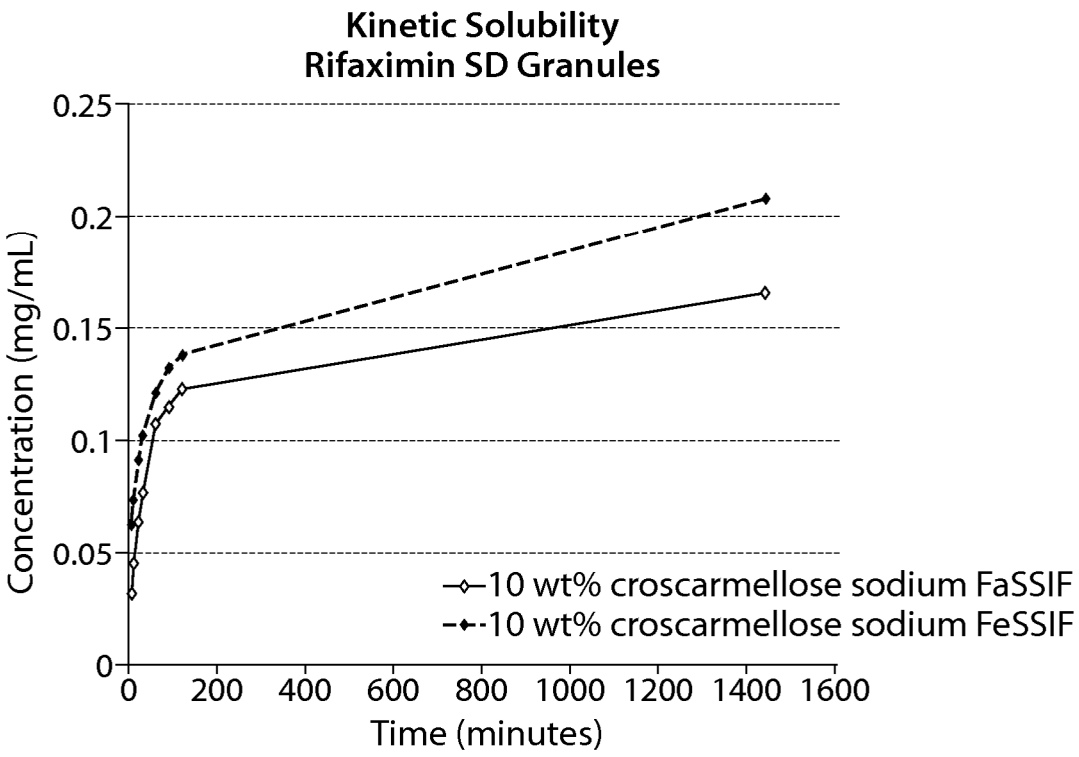


Fig. 65A

Rifaximin SDD with 10% CS Formulation was Used in Human Clinical Studies

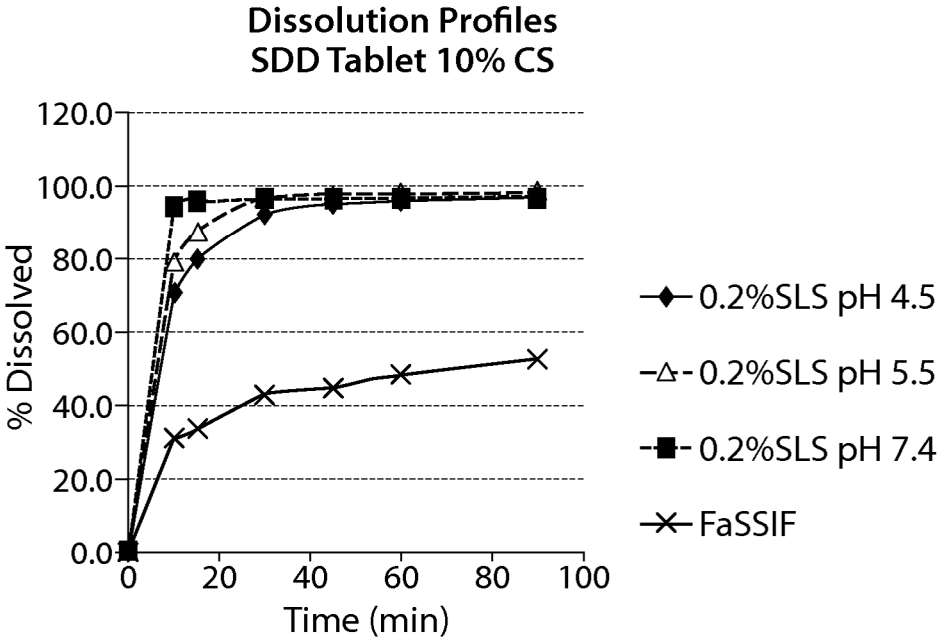


Fig. 65B

Rifaximin SDD with 10% CS Formulation was used in Human Clinical Studies

Rifaximin SDD Capsules Dissolution
Acid Phase: 2 Hours; Buffer Phase: p. Buffer pH 7.4

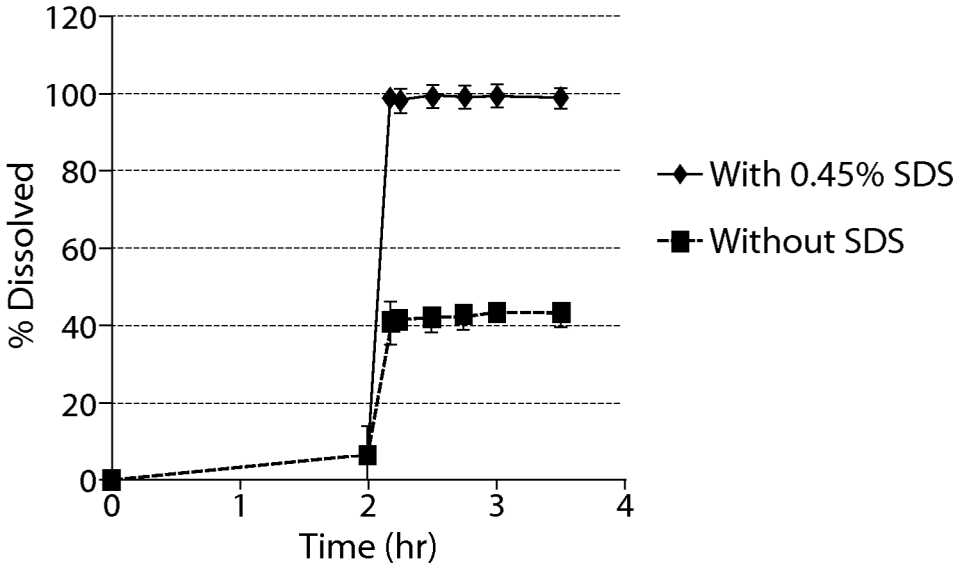


Fig. 66A

Rifaximin SDD with 10% CS Formulation was used in Human Clinical Studies

Rifaximin SDD Capsules Dissolution
Acid Phase: 0.1 N HCl with variable exposure time
Buffer Phase: P. Buffer pH 7.4 W/0.45% SDS

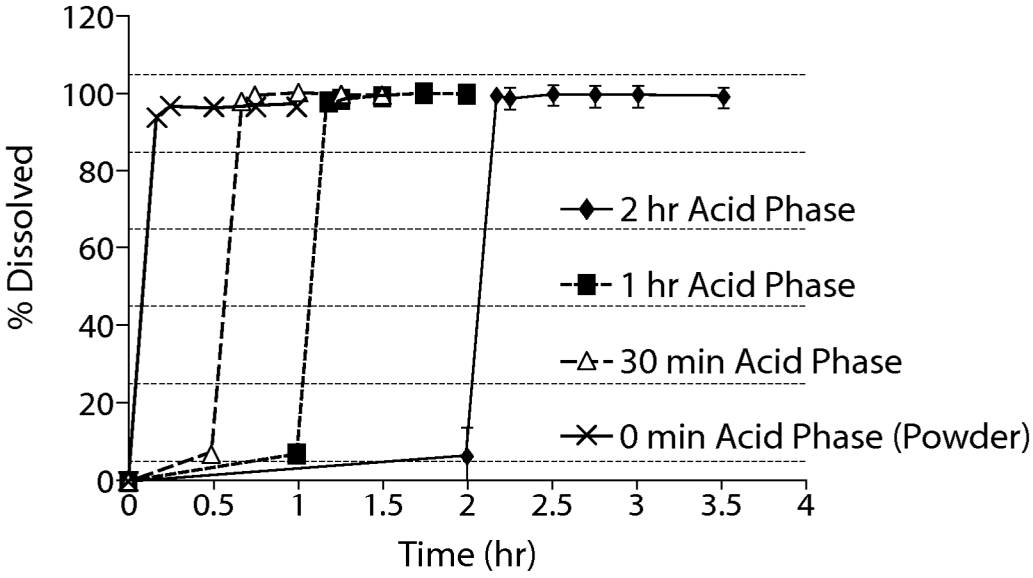


Fig. 66B

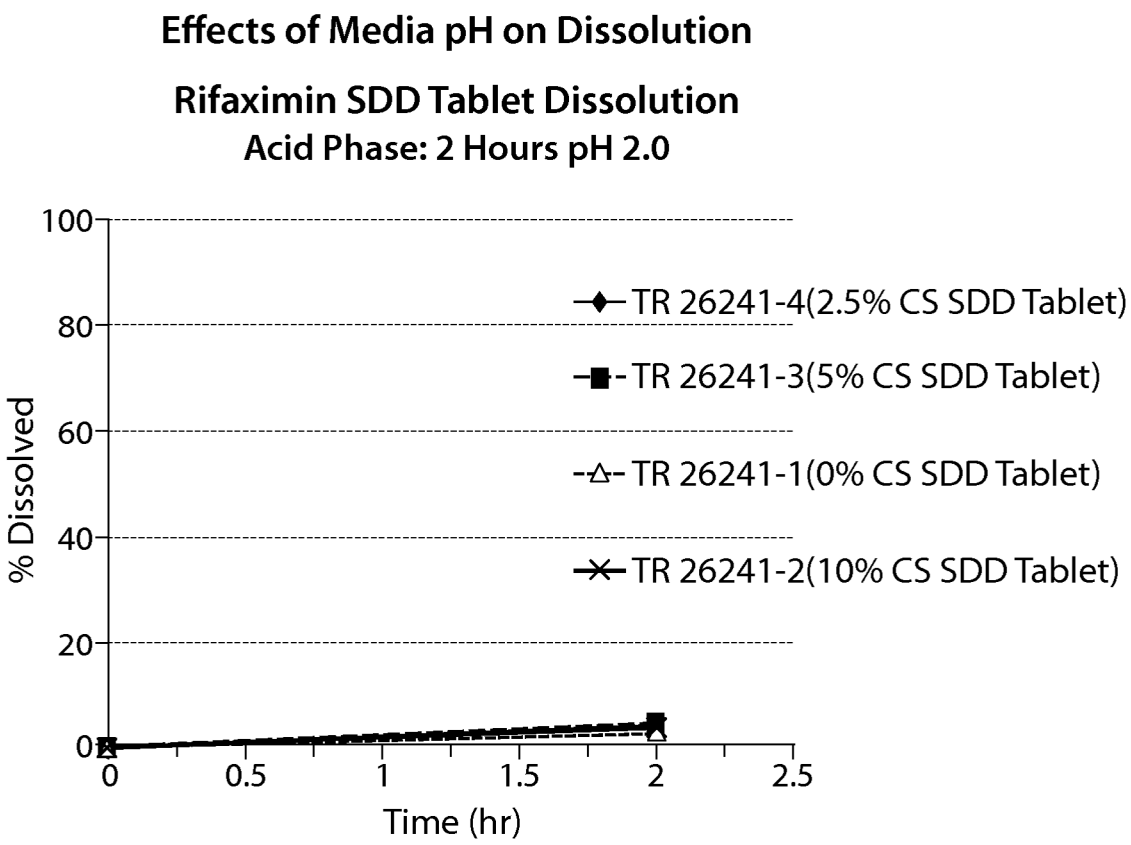


Fig. 67A

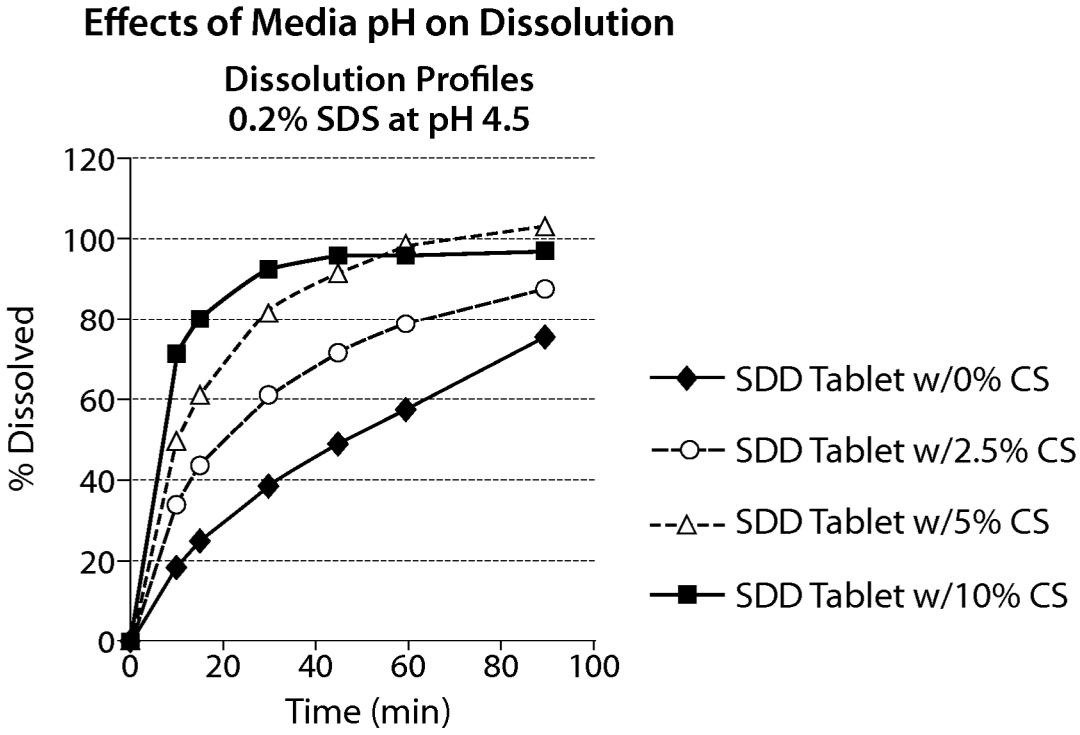


Fig. 67B

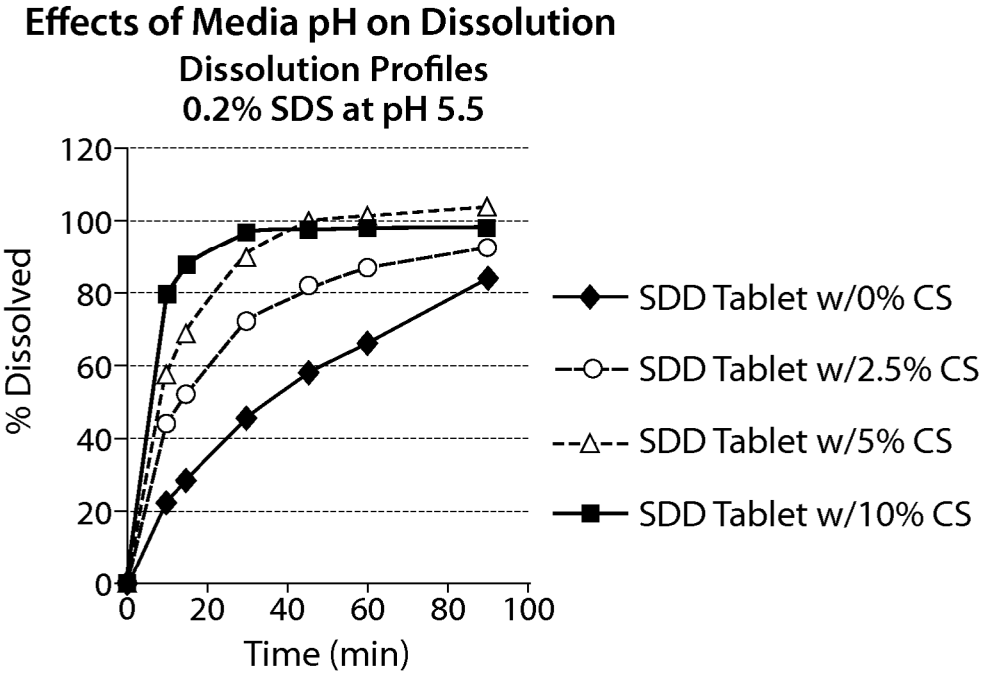


Fig. 68A

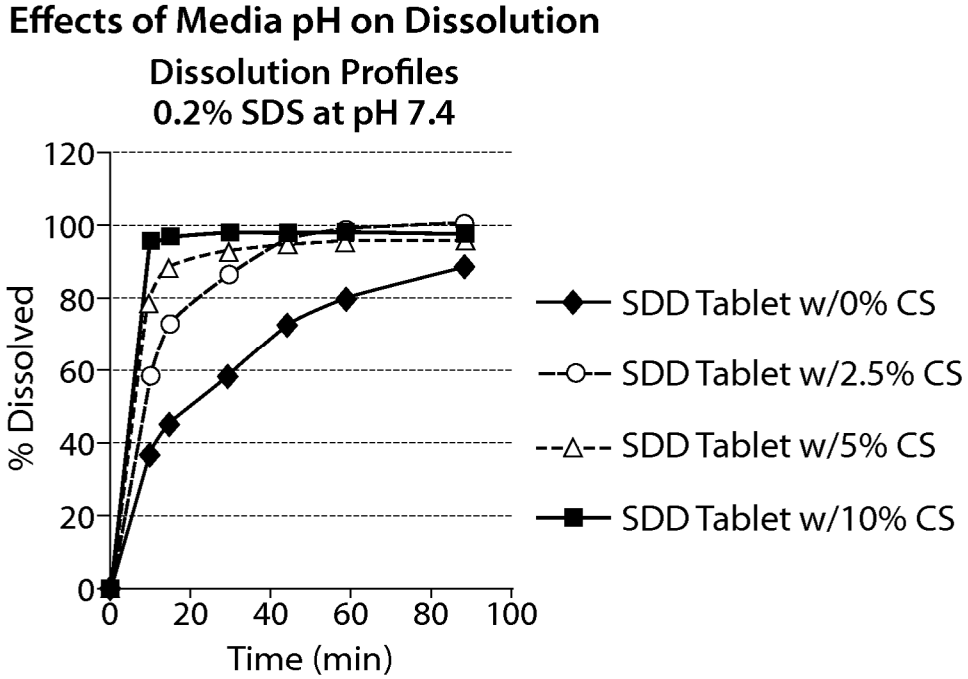


Fig. 68B

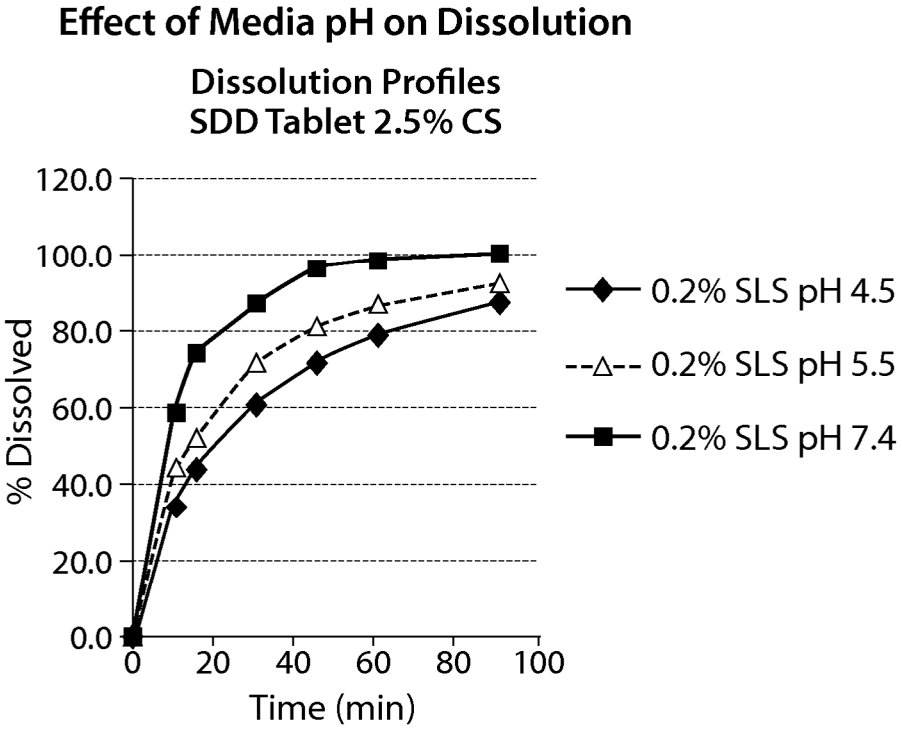


Fig. 69A

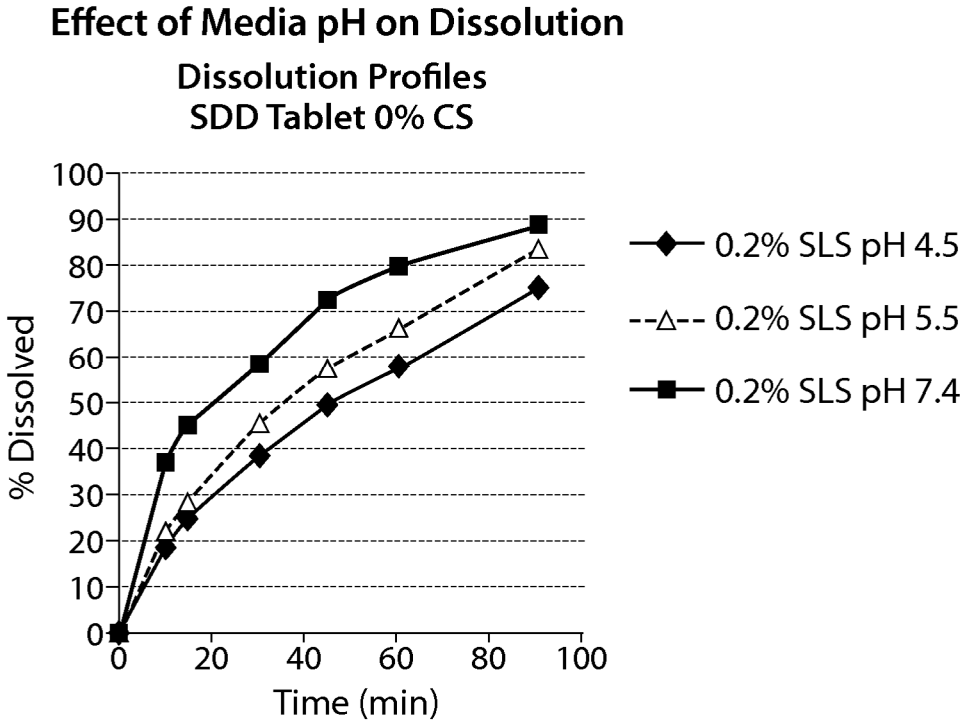


Fig. 69B

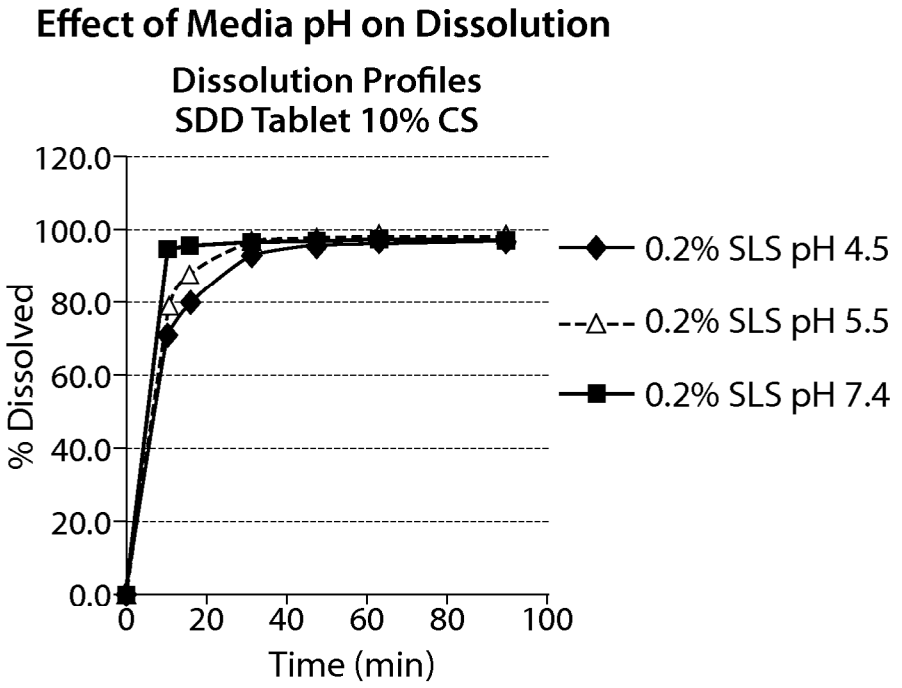


Fig. 70A

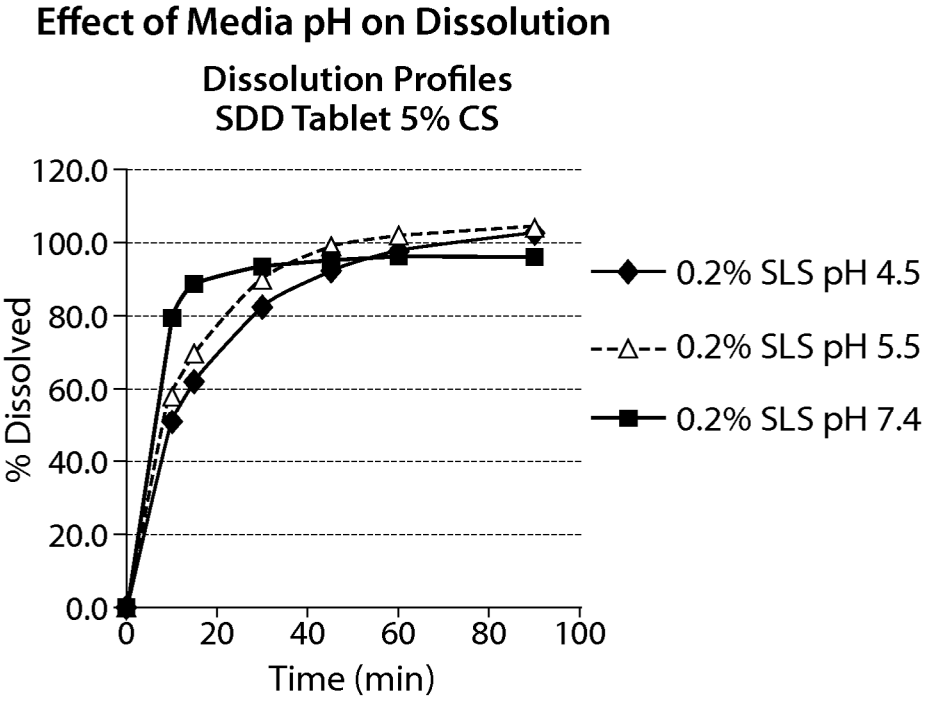


Fig. 70B

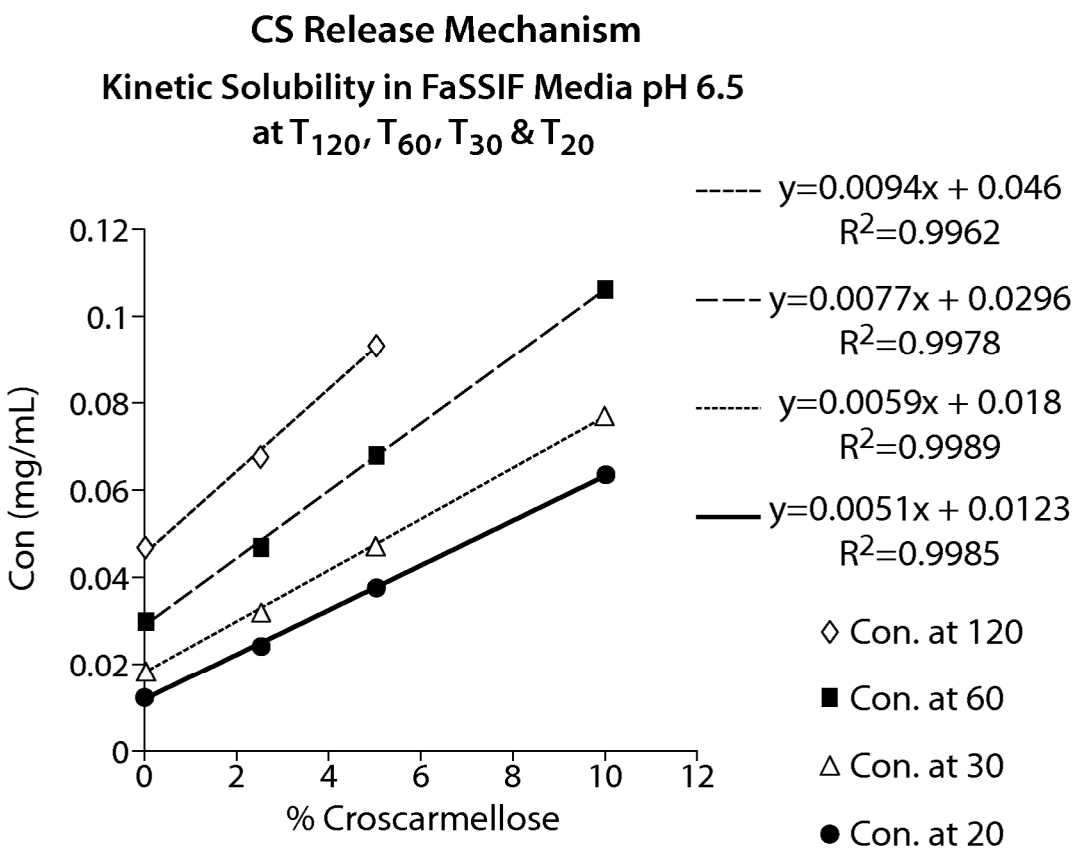


Fig. 71A

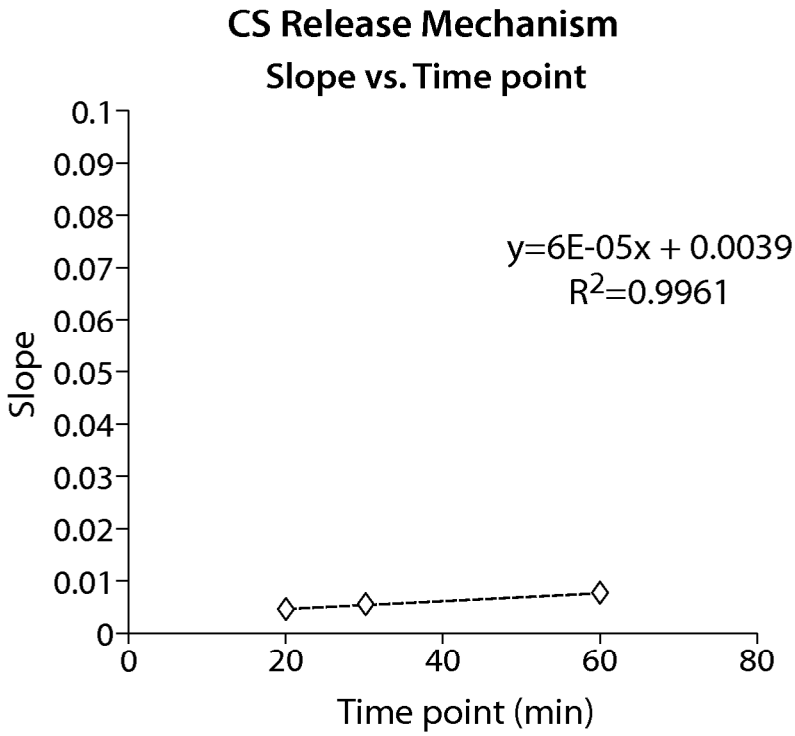


Fig. 71B

Overlay of XRPD patterns of rifaximin quaternary samples dried from methanol

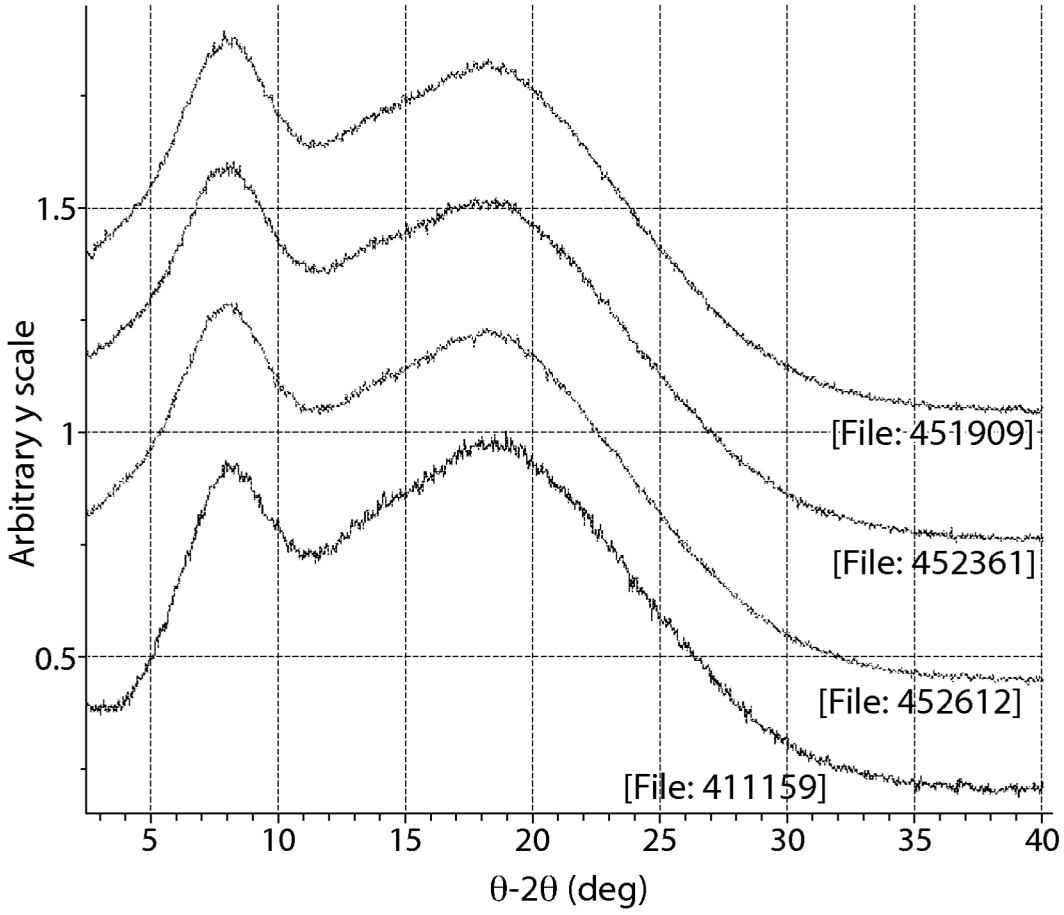


Fig. 72

mDSC thermogram of rifaximin quaternary sample containing 0.063 wt% BHA

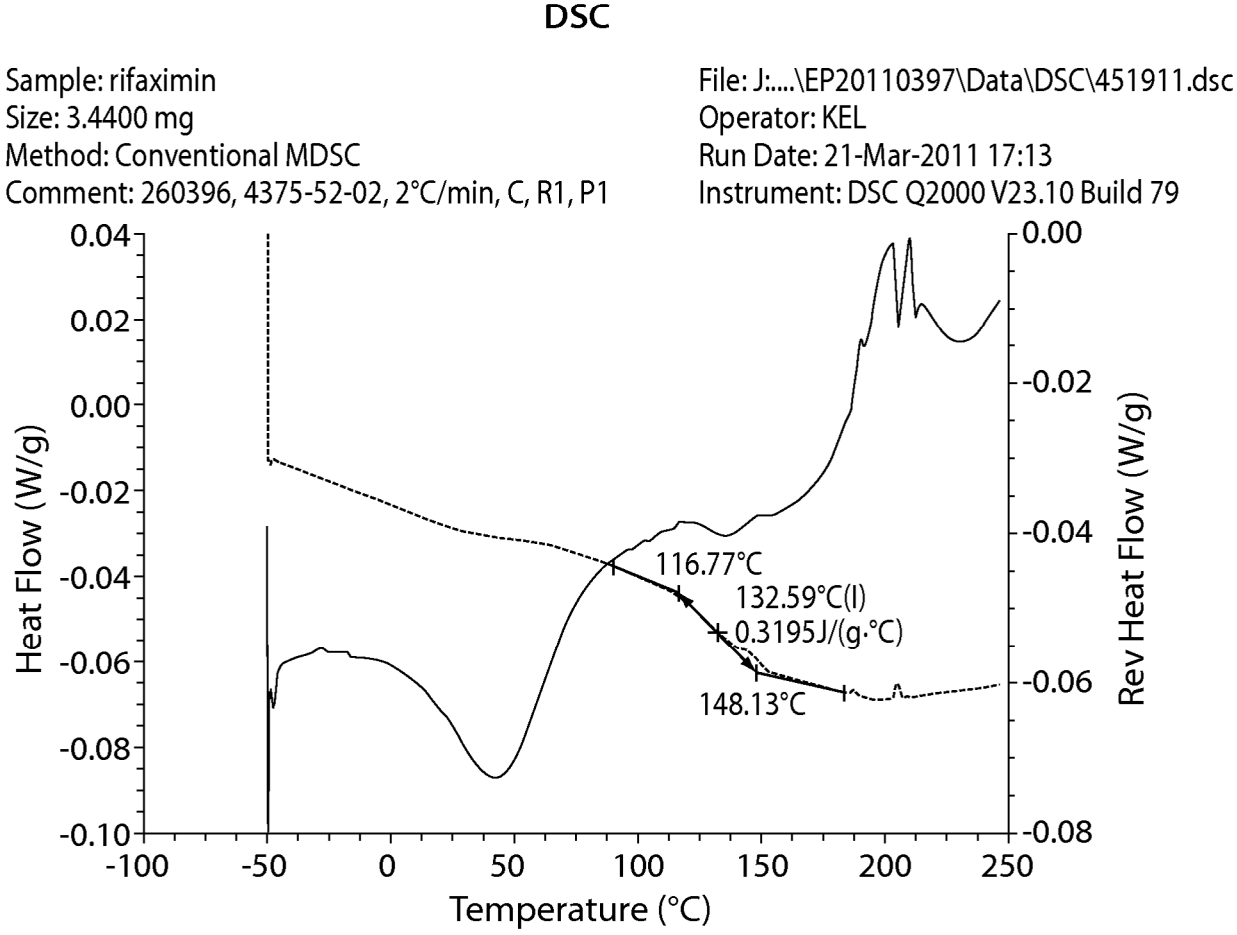


Fig. 73

mDSC thermogram of rifaximin quaternary sample containing 0.063 wt% BHT

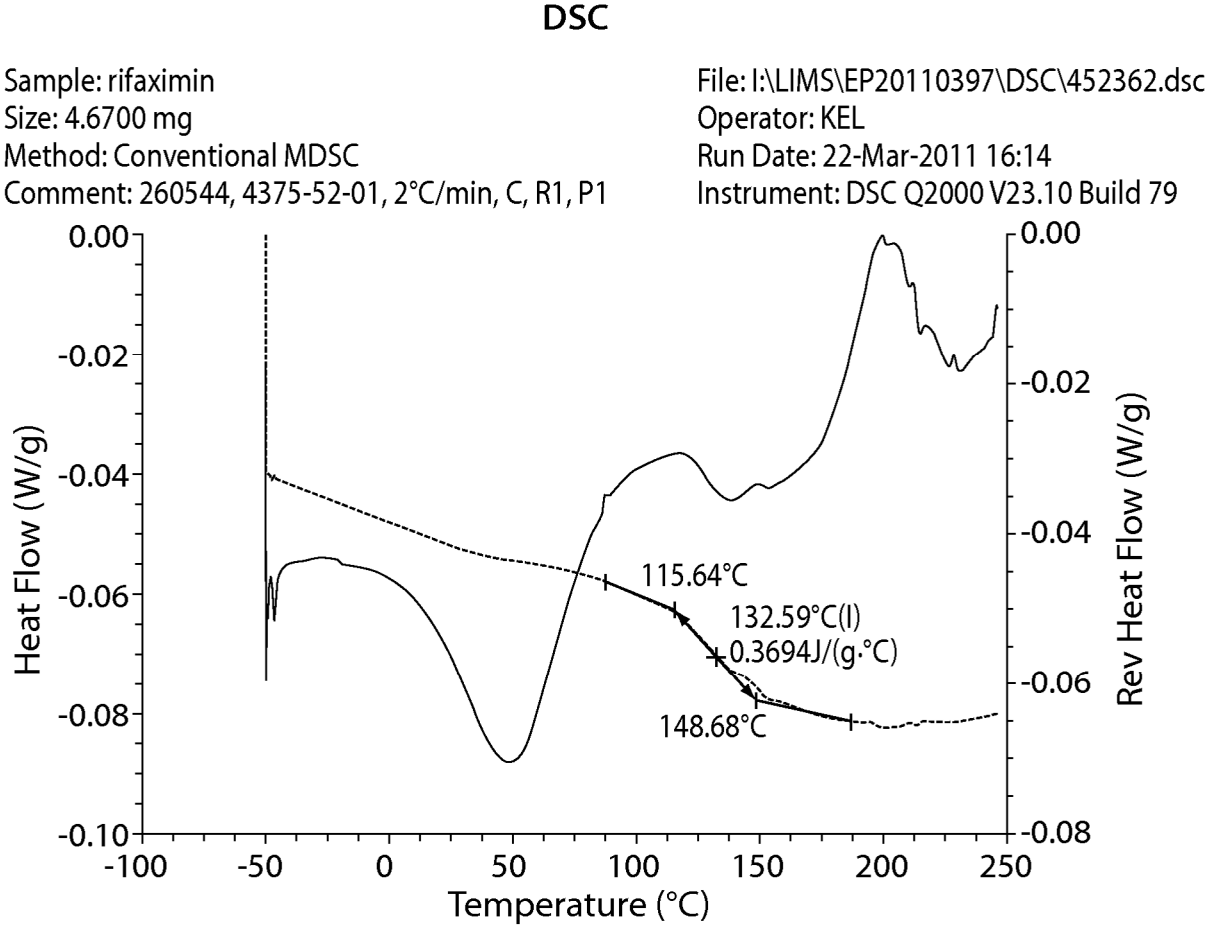


Fig. 74

mDSC thermogram of rifaximin quaternary sample containing 0.094 wt% PG

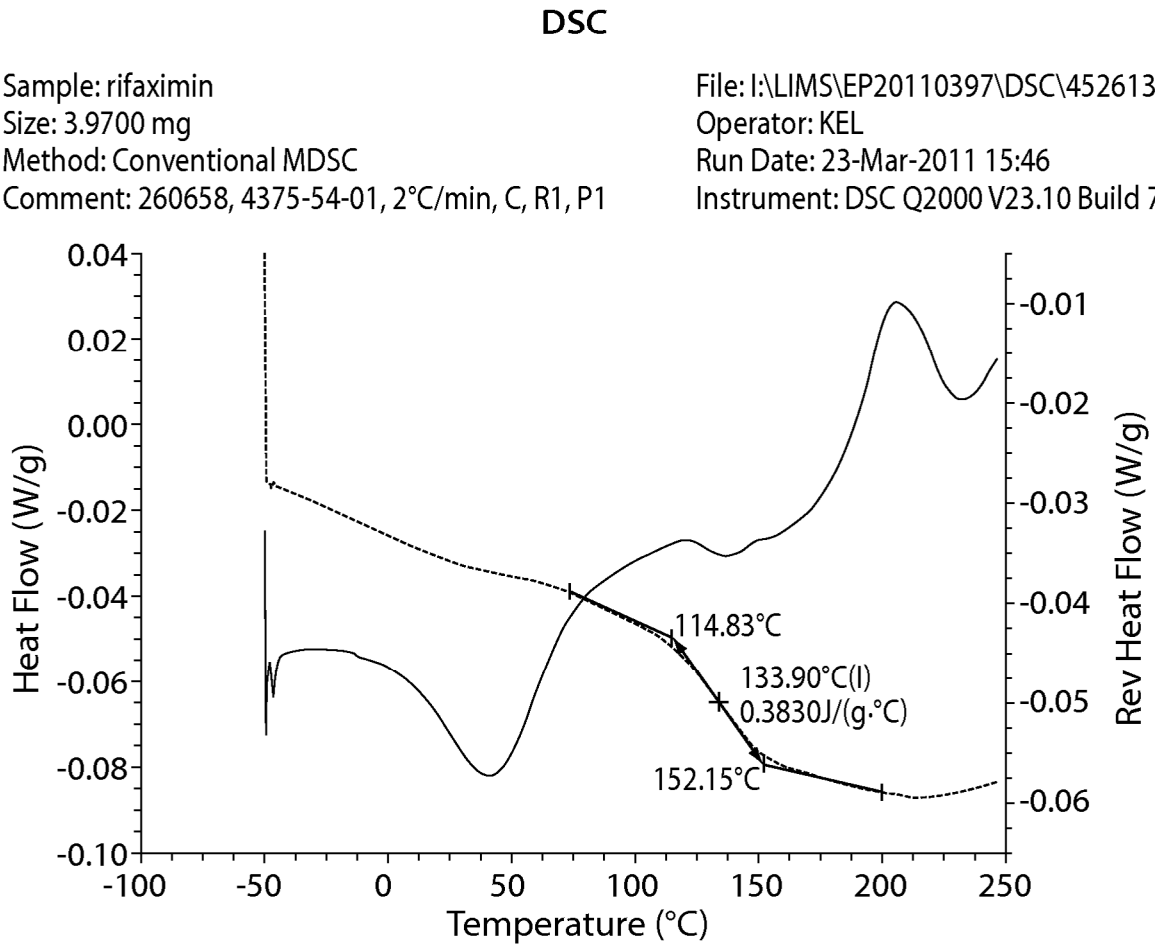


Fig. 75

XRPD pattern comparison of rifaximin solid dispersion powder 42.48% w/w with roller compacted material

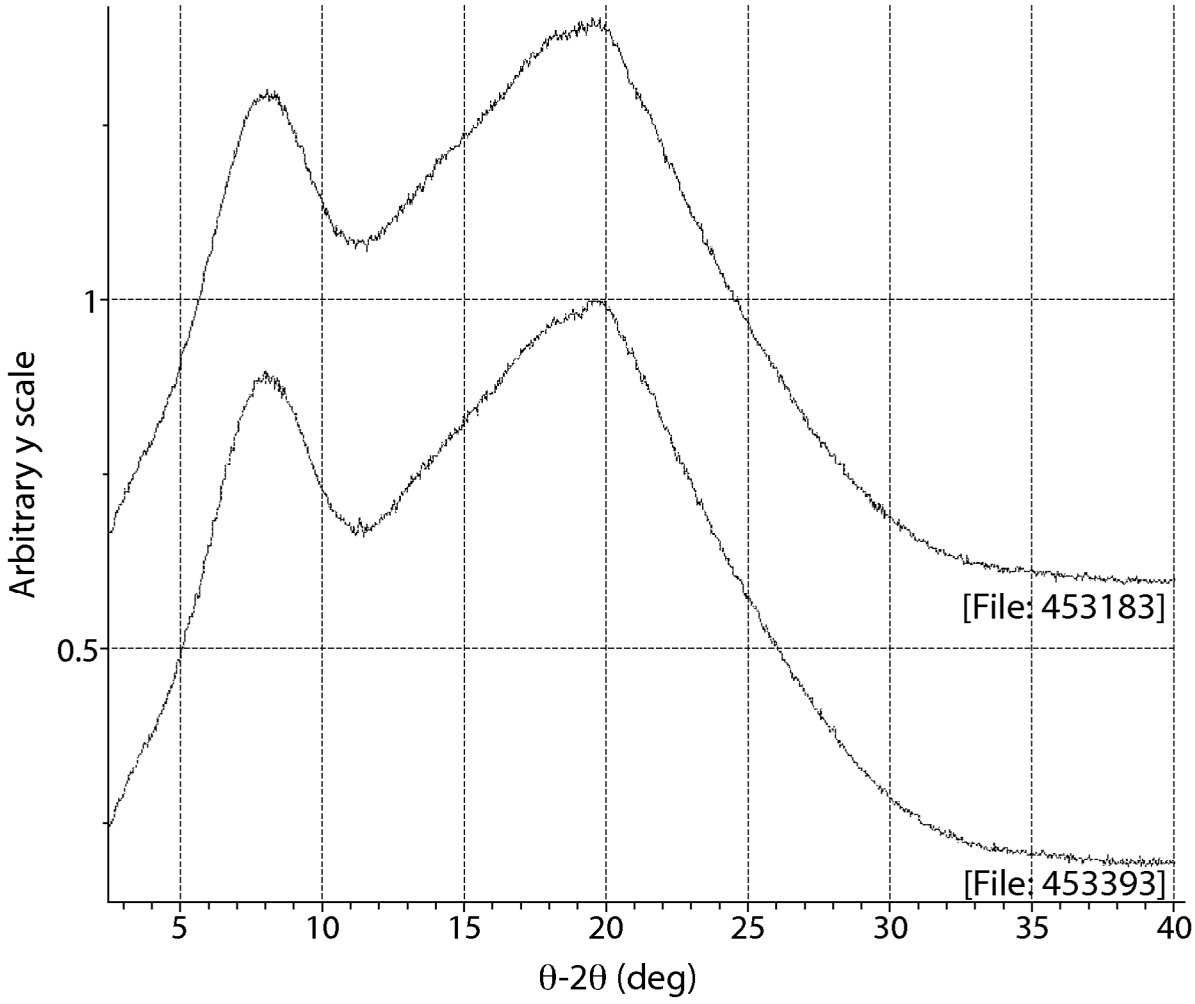


Fig. 76

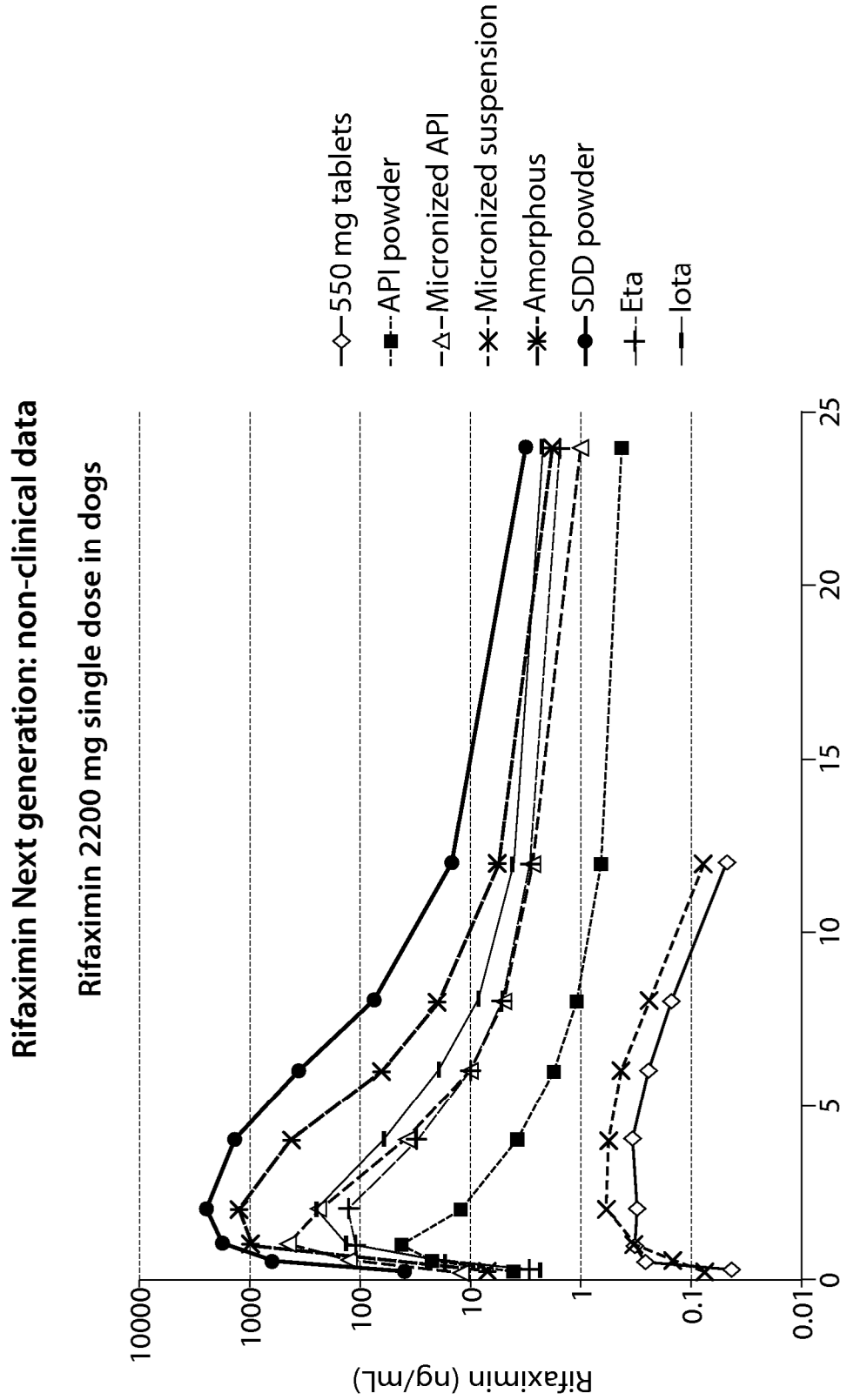
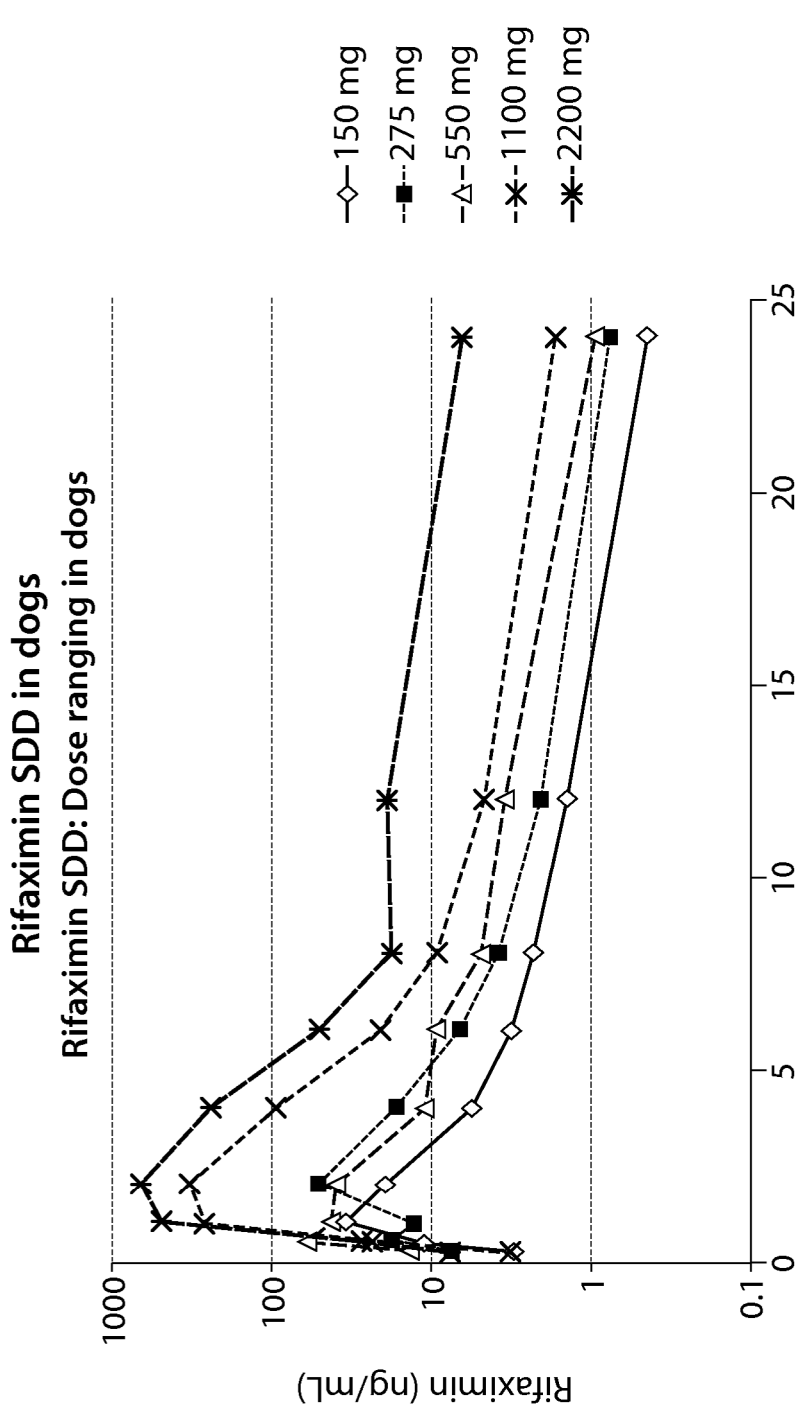

Rifaximin Next generation: non-clinical data
Rifaximin 2200 mg single dose in dogs
550 mg tablets
API powder
Micronized API
Micronized suspension
Amorphous
SDD powder
Eta
Iota
Rifaximin (ng/mL)
10000
1000
100
10
1
0.1
0.01
0
5
10
15
20
25
Time (h)

Fig. 77



SDD dose (mg)	Dose Multiple	$T_{1/2}$ (h)	T_{max} (h)	C_{max} (ng/mL)	C_{max} multiple	AUC_{0-24} (ng.h/mL)	AUC Multiple
150	1	6.1	1	35.2	1	95.2	1
275	1.8	7	1.5	59	1.7	169.1	1.8
550	3.7	5.1	0.75	80.9	2.3	200.0	2.1
1100	7.3	4.3	1.5	431	12.2	983.7	10.3
2200	14.7	5.3	2	700	19.9	2165.8	22.75

Fig. 78

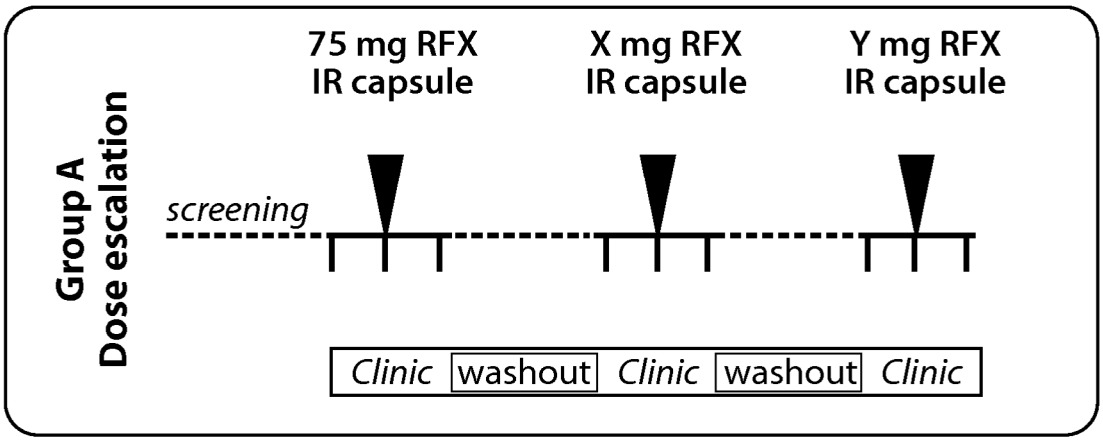


Fig. 79

Part A dose escalation / dose selection

– N = 10 male subjects
– 3 ascending single doses (SDD powder in capsule)
  • 75, 250, 550 mg planned
– Plasma PK samples collected fpr 24 h
– Urine and feces collected in total for 24 h
– ~7 day washout between doses
– Safety, tolerability, and plasma PK data reviewed at each decision point for next dose selection

Fig. 80

Example SDD dose escalation: Subject 001

Dose	Dose multiple	$T_{1/2}$ (h)	T_{max} (h)	C_{max} (ng/mL)	C_{max} multiple	AUC_{0-24} (ng.h/mL)	AUC_{0-24} multiple
75 MG IR	1	15.7	0.5	4.1	1.0	11.2	1.0
250 MG IR	3.3	7.6	0.5	8.2	2.0	21.7	1.9
550 MG IR	7.3	10.6	1	23.1	5.7	66.4	5.9

Fig. 81

Example SDD dose escalation: Subject 006

Dose	Dose multiple	$T_{1/2}$ (h)	T_{max} (h)	C_{max} (ng/mL)	C_{max} multiple	AUC_{0-24} (ng.h/mL)	AUC_{0-24} multiple
75 MG IR	1	5.1	1.5	8.4	1	24.7	1
250 MG IR	3.3	7.6	1	22.0	2.6	67.2	2.7
550 MG IR	7.3	10.2	3	58.8	7	234.1	9.5

Fig. 82

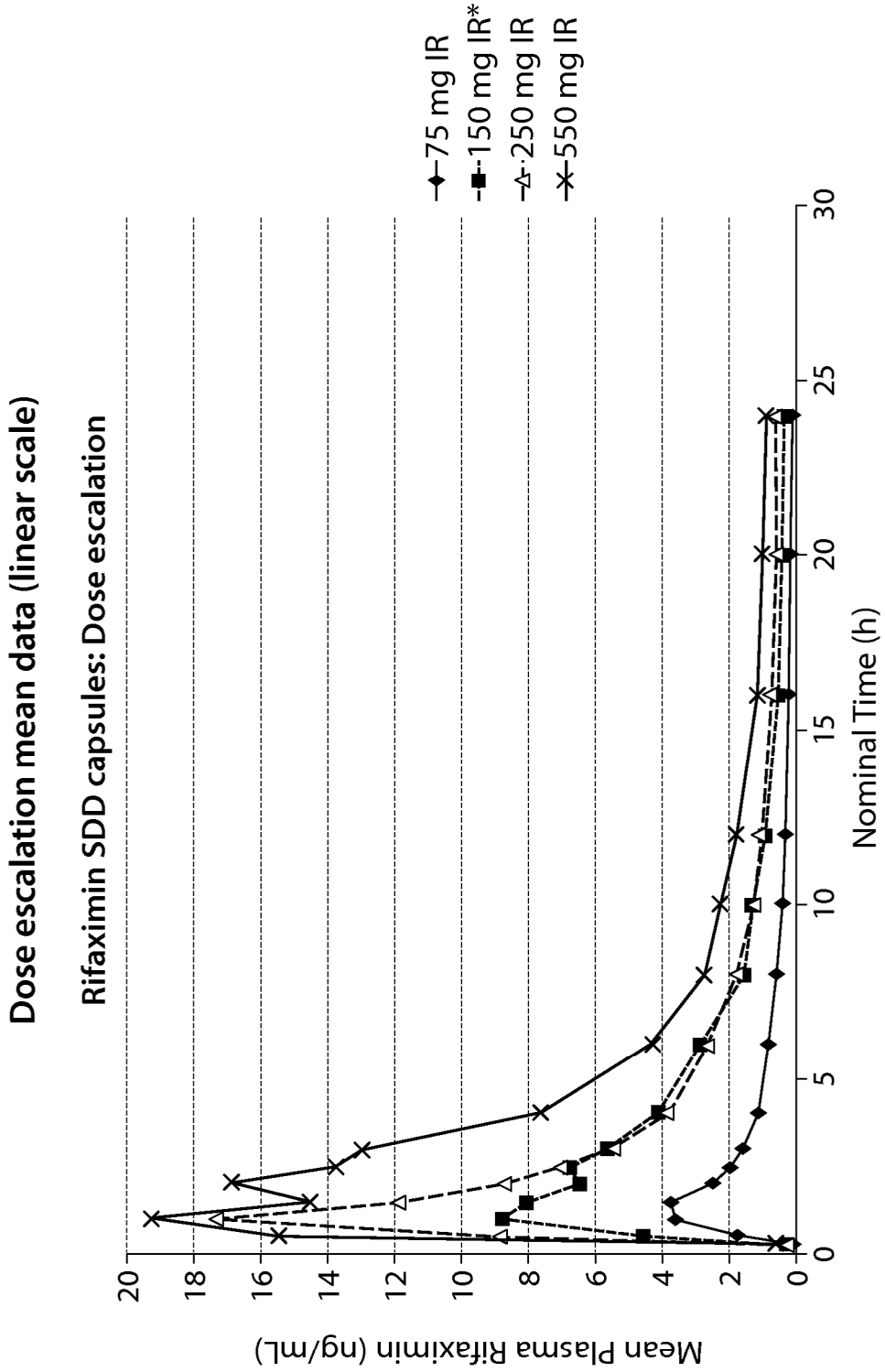

Dose escalation mean data (linear scale)
Rifaximin SDD capsules: Dose escalation
75 mg IR
150 mg IR*
250 mg IR
550 mg IR
Mean Plasma Rifaximin (ng/mL)
Nominal Time (h)
0
2
4
6
8
10
12
14
16
18
20
0
5
10
15
20
25
30

Fig. 83

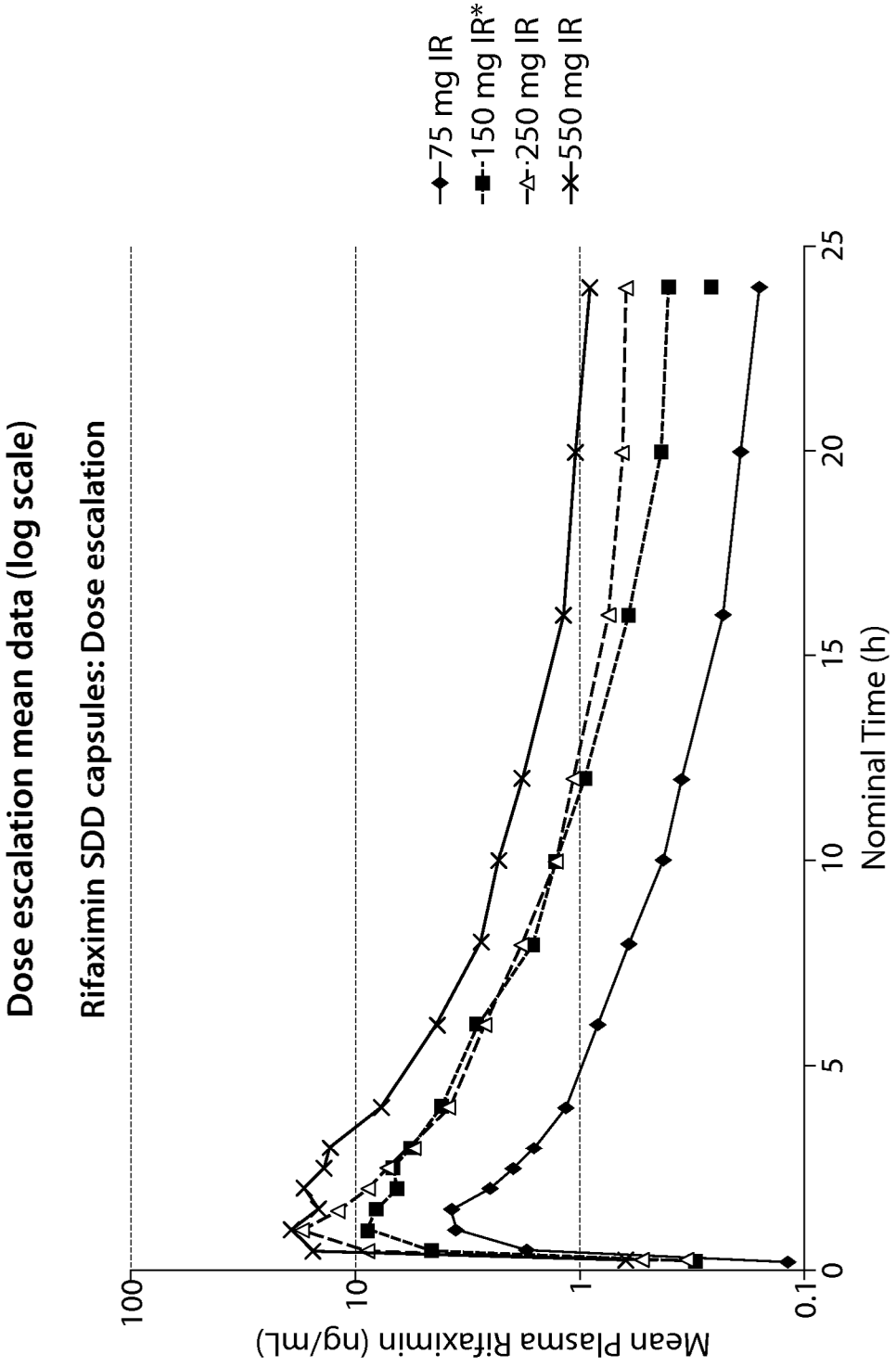
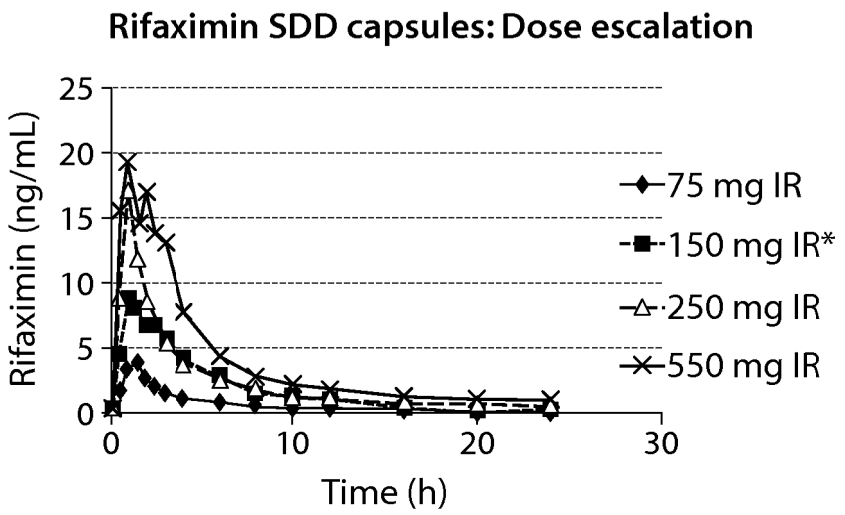
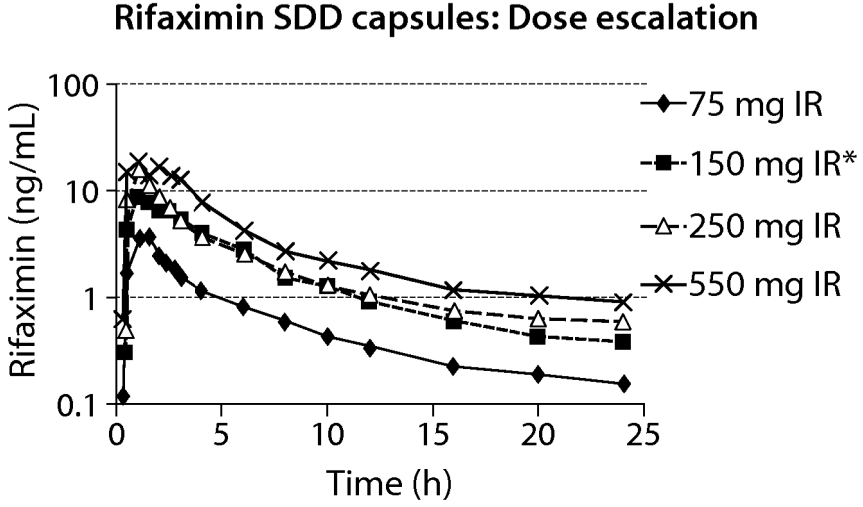

Dose escalation mean data (log scale)
Rifaximin SDD capsules: Dose escalation
75 mg IR
150 mg IR*
250 mg IR
550 mg IR
Mean Plasma Rifaximin (ng/mL)
100
10
1
0.1
0
5
10
15
20
25
Nominal Time (h)

Fig. 84

Rifaximin SDD dose escalation summary





Mean Pk parameters Dose	Dose multiple	$T_{1/2}$ *(h)	T_{max} **(h)	C_{max} (ng/mL)	C_{max} multiple	AUC_{0-24} (ng.h/mL)	AUC_{0-24} multiple	% of dose in urine (0-24)
75 MG IR	1	9.2	1.25	4.8	1	16.1	1	0.21
150 MG IR	2	9.2	2.5	12.5	2.6	47.6	3.0	-
250 MG IR	3.3	12.8	1	19.9	4.1	62.9	3.9	0.18
550 MG IR	7.3	12.9	1	25.5	5.3	98.7	6.1	0.13

Fig. 85

SUBSTITUTE SHEET (RULE 26)

Dose/dosage form comparison

Mean PK parameters:

Formulation and conditions	Dose	$T_{1/2}$* (h)	T_{max}** (h)	C_{max} (ng/mL)	AUC_{0-24} (ng.h/mL)
SDD in gelatin capsules, healthy	75 MG	9.2	1.25	4.8	16.1
	150 MG	9.2	2.5	12.5	47.6
	250 MG	12.8	1	19.9	62.9
	550 MG	12.9	1	25.5	98.7
Marketed tablet, healthy (RFPK1007)	550 MG	1.8	0.75	4.0	11.1¤
Marketed tablet, IBS	550 MG	3.1	0.775	3.5	9.7§
Marketed tablet, C-P A	550 MG	8.1	1	19.5	118§
Marketed tablet, C-P B	550 MG	10.5	1	25.1	161§
Marketed tablet, C-P C	550 MG	6.6	1	35.5	246§

*Geometric mean; **Median; §AUC(0-12h); ¤AUC(0-∞)

Fig. 86

SUBSTITUTE SHEET (RULE 26)

Dose/dosage form comparison

Mean PK parameters: 6.4-fold difference in C_{max}

~8.9-fold difference in AUC

Formulation and conditions	Dose (mg)	$T_{1/2}$* (h)	T_{max}** (h)	C_{max} (ng/mL)	AUC_{0-24} (ng.h/mL)
SDD in gelatin capsules, healthy	75	9.2	1.25	4.8	16.1
	150	9.2	2.5	12.5	47.6
	250	12.8	1	19.9	62.9
	550	12.9	1	25.5	98.7
Marketed tablet, healthy (RFPK1007)	550	1.8	0.75	4.0	11.1¤
Marketed tablet, IBS	550	3.1	0.775	3.5	9.7§
Marketed tablet, C-P A	550	8.1	1	19.5	118§
Marketed tablet, C-P B	550	10.5	1	25.1	161§
Marketed tablet, C-P C	550	6.6	1	35.5	246§

*Geometric mean; **Median; §AUC(0-12h); ¤AUC(0-∞)

Fig. 87