Electronic Supplementary Information (ESI)

Crystalline salts of a diuretic drug Torasemide with improved solubility and dissolution properties.

Monika Garg,[a] Mayank K. Singh,[b] Saylee Manohar Koli,[a] Bojja Sreedhar[c,d] Sistla Ramakrishna,*[b,d] Jagadeesh Babu Nanubolu*[a,d]

[a]Centre for X-ray Crystallography, Department of Analytical & Structural Chemistry, CSIR-Indian Institute of Chemical Technology, Tarnaka, Uppal Road, Hyderabad-500007, Telangana, India.

[b]Department of Applied Biology, CSIR-Indian Institute of Chemical Technology, Tarnaka, Uppal Road, Hyderabad-500007, Telangana, India.

[c]Department of Analytical & Structural Chemistry, CSIR-Indian Institute of Chemical Technology, Tarnaka, Uppal Road, Hyderabad-500007, Telangana, India.

[d]Academy of Scientific and Innovative Research (AcSIR), New Delhi, 110025, India

Table of Contents of ESI

Table S1. Crystal structures, canonical states and intramolecular hydrogen bonds

S.No	CSD Refcodes	Label	Conformations	Neutral/ionic	Intramolecular H- Bond, represented by graph-set notation
1	TORSEM TORSEM02 TORSEM05	Polymorph T-I	2	Neutral Zwitterionic	S8 motif, N–H···O=C S6 motif, N–H···O=S
2	TORSEM01	T-II It is a solvate	2	Zwitterionic Zwitterionic	S6 motif, N–H···N^-–S S6 motif, N–H···N^-–S
3	TORSEM03 TORSEM04 TORSEM06 TORSEM07	Polymorph T-N/T-III	2	Zwitterionic Zwitterionic	S6 motif, N–H···N^-–S S6 motif, N–H···N^-–S
4	QOVDUB	Torasemide methanol solvate hydrate	2	Zwitterionic Zwitterionic	S6 motif, N–H···N^-–S S6 motif, N–H···N^-–S
5	UKIFIE	Torasemide hydrochloride	3	Ionic Ionic Ionic	S6 motif, N–H···O=S S8 motif, N–H···O=C S8 motif, N–H···O=C

Table S2. ΔpKa values of between the drug torasemide and coformer molecules.

S.No	**Compound**	**pKa_1**	**ΔpKa[$]**	**Is ΔpKa > 3**
1	Oxalic acid	1.23	5.87	Yes
2	Succinic acid	4.2	2.90	No; very close to 3
3	Fumaric acid	3.03	4.07	Yes
4	Tartaric acid	2.98	4.12	Yes
5	Citric acid	3.14	3.96	Yes
6	Salicylic acid	2.97	4.13	Yes
7	Benzoic acid	3.20	3.90	Yes
8	*p*-Toluene sulfonic acid	-2.1	9.20	Yes

*pKa of torasemide is 7.1

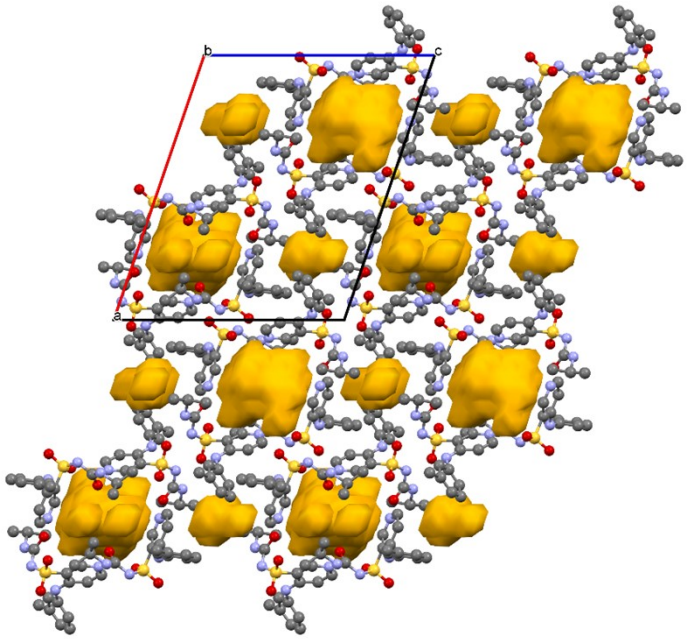
[$]ΔpKa = pKa of torasemide - pKa of coformer (**7.1 -** pKa of coformer**)**

Table S3. Dissolution studies of torasemide polymorph T-I, polymorph T-III/T-N and torasemide fumarate (TRS-FUM) and torasemide oxalate (TRS-OX) salts in simulated gastric fluid 0.1 N HCl solution (pH 1.2). The % of drug dissolved as a function of time is given below.

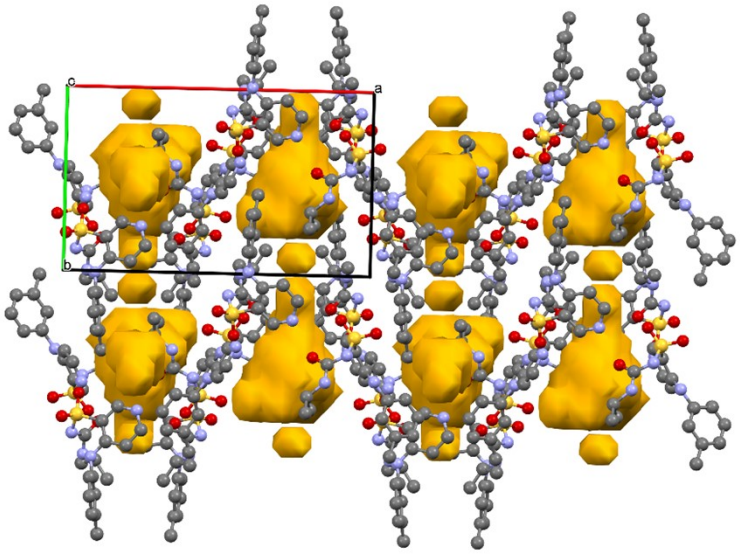
Time (min)	T-I (%)	T-III/T-N (%)	TRS-FUM-1:1 (%)	TRS-OX-2:1 (%)
0	0	0	0	0
1	31.13	42.72	57.50	50.48
2.5	37.70	51.61	71.18	67.69
5	47.40	62.45	83.73	76.11
7.5	50.75	63.26	88.85	81.08
10	54.88	66.89	90.67	86.62
12.5	57.30	70.22	93.49	90.54
15	57.21	74.21	93.84	91.80
20	58.59	75.18	94.00	93.40
25	58.48	75.14	94.96	93.47
30	58.17	74.94	96.34	93.81
45	58.88	75.20	96.78	93.07
60	58.07	75.98	96.62	94.11

Table S4. Dissolution studies of torasemide polymorph T-I, polymorph T-III/T-N and torasemide fumarate (TRS-FUM) and torasemide oxalate (TRS-OX) salts in phosphate buffer (pH 6.8). The % of drug dissolved as a function of time is given below.

Time (min)	T-I (%)	T-III/T-N (%)	TRS-FUM-1:1 (%)	TRS-OX-2:1 (%)
0	0	0	0	0
1	33.35	45.55	55.15	50.16
2.5	46.70	55.89	62.45	55.07
5	53.57	69.06	70.88	60.73
7.5	64.25	82.11	77.70	68.83
10	65.22	85.71	85.47	75.99
12.5	66.91	85.58	90.01	90.99
15	66.65	85.69	93.10	91.10
20	66.92	85.62	93.45	91.81
25	66.98	85.22	93.13	91.25
30	66.75	85.00	93.98	91.37
45	66.77	85.51	93.96	91.77
60	66.55	85.96	93.31	91.89

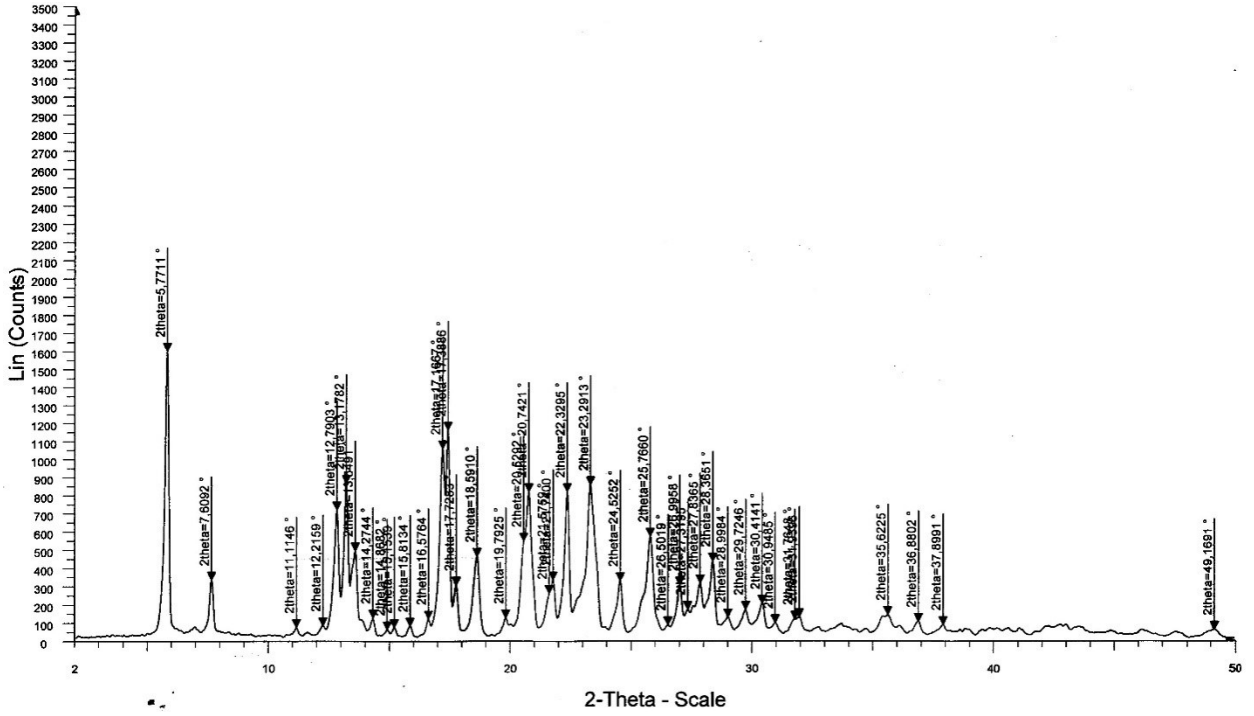


(a)

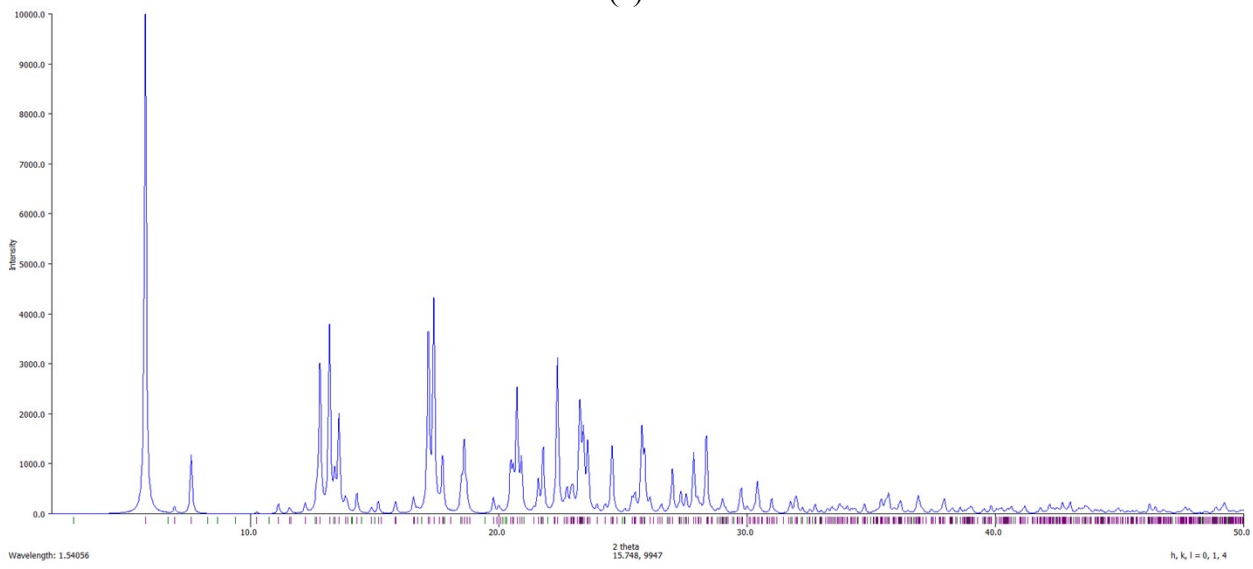


(b)

Figure S1. Crystal packing diagram of torasemide Form II (CSD refcode TORSEM01) showing inherent voids (empty spaces)in the crystal lattice, viewed along the (a) *b*-axis (b) *c*-axis. The void volume is 320.6Å^3 which constitutes to 8.5% of the unit cell volume (V = 3791.87Å^3). Images were generated using "Voids" software module of CCDC Mercury 4.3.1 (Build 273970)) using the default parameters of 1.2Å probe radius and 0.7Å grid spacing.

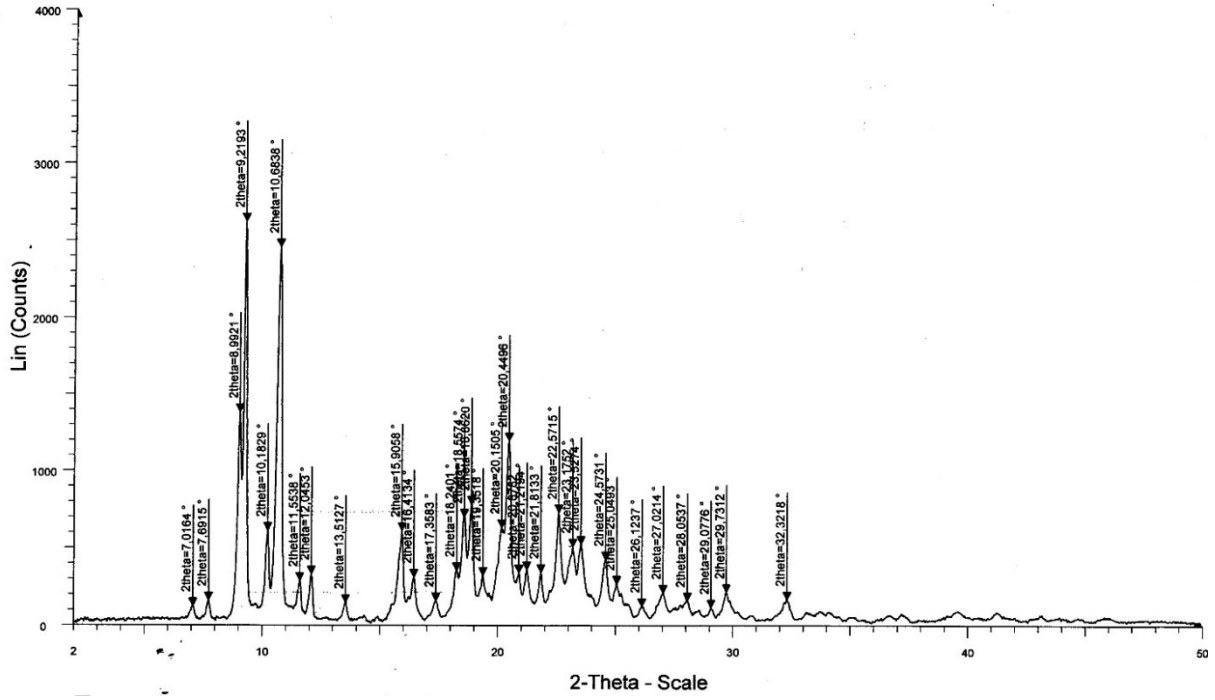


(a)

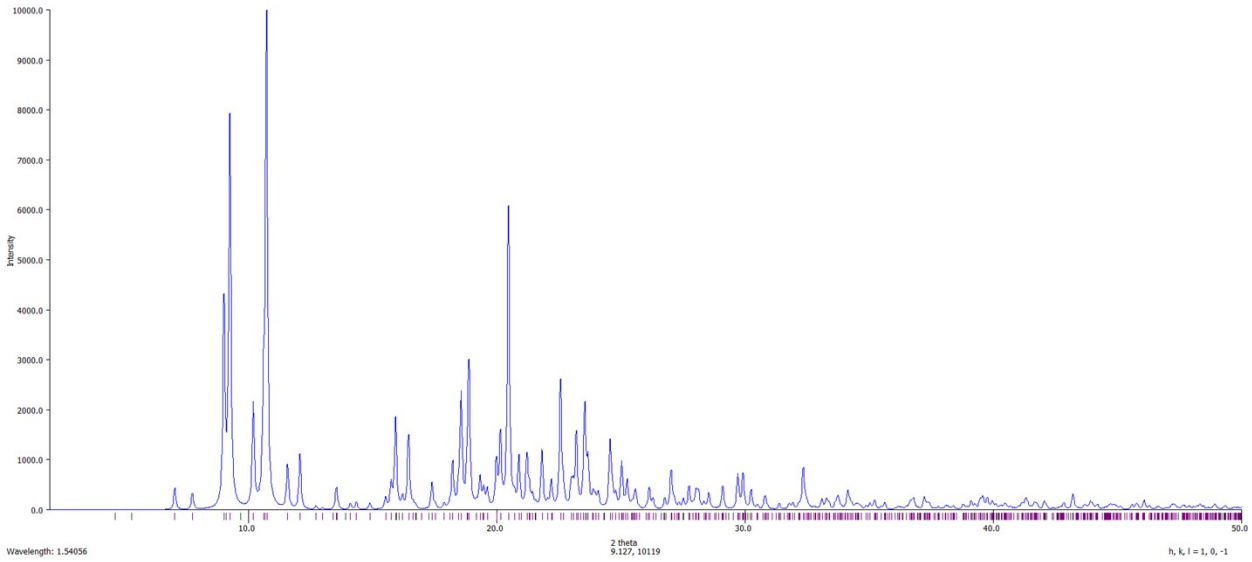


(b)

Figure S2. (a) Experimental PXRD pattern of form I of torasemide (b) Simulated PXRD pattern of form I of torasemide generated from CSD Refcode TORSEM (image generated in CCDC Mercury 4.3.1 (Build 273970))

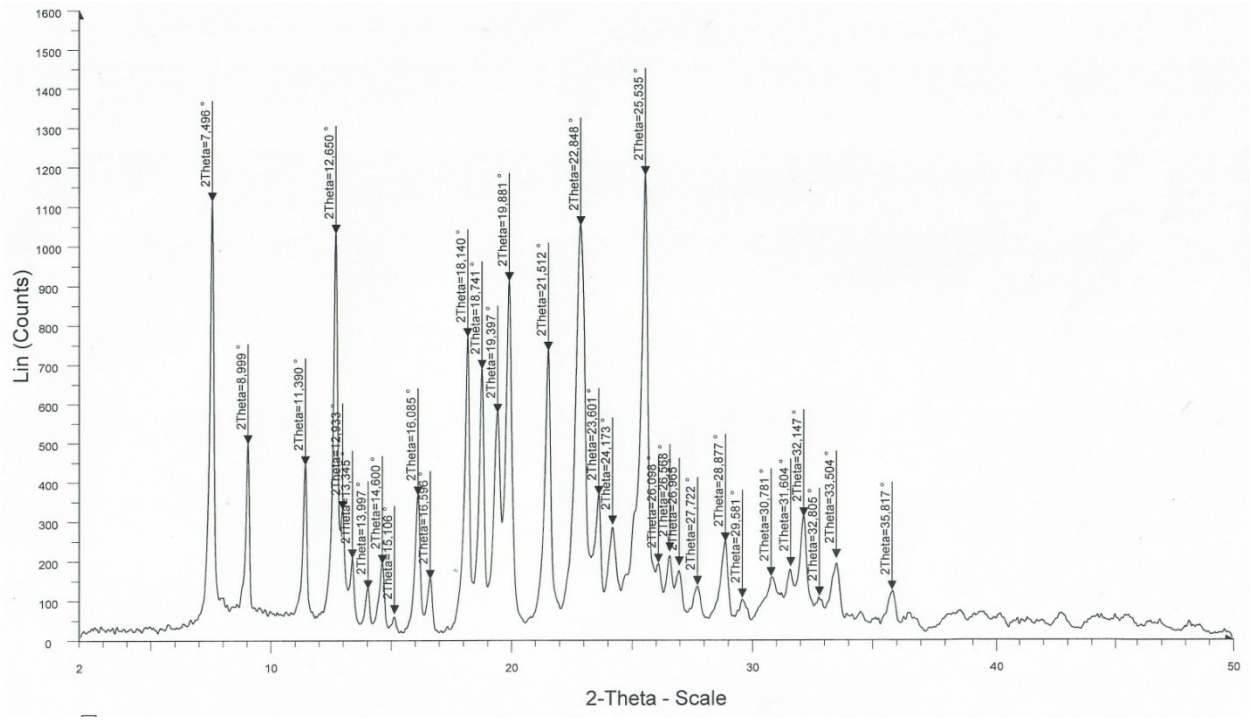


(a)

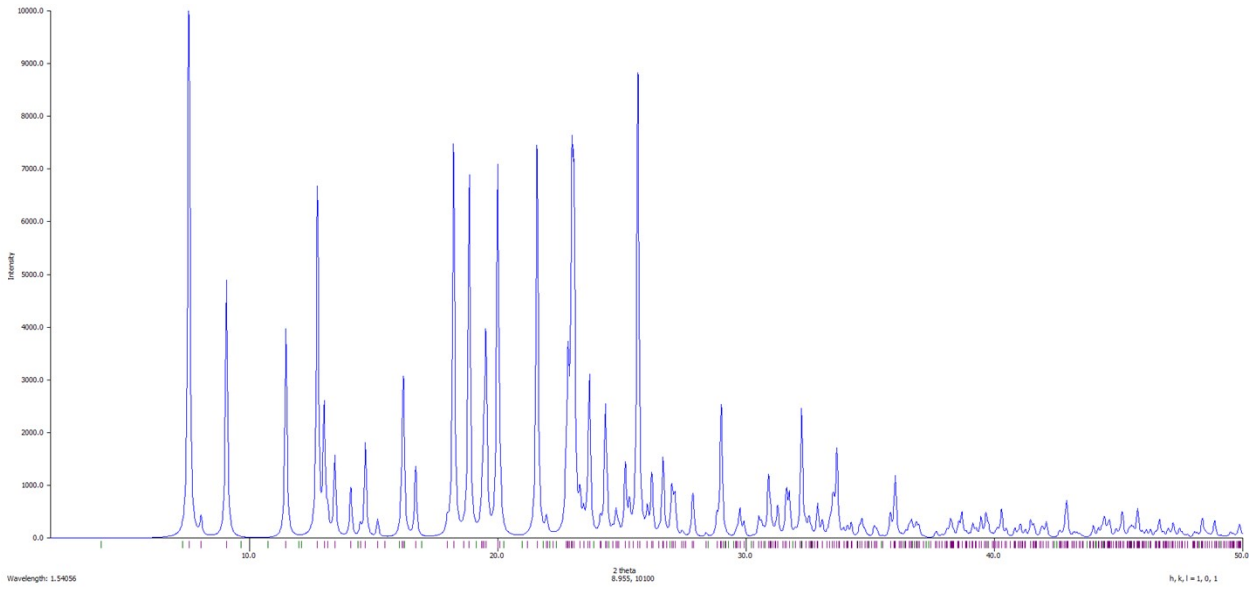


(b)

Figure S3. (a) Experimental PXRD pattern of T-III/T-N polymorph of torasemide. (b) Simulated PXRD pattern of T-III/T-N polymorp of torasemide generated from CSD Refcode TORSEM03 (image generated in CCDC Mercury 4.3.1 (Build 273970))

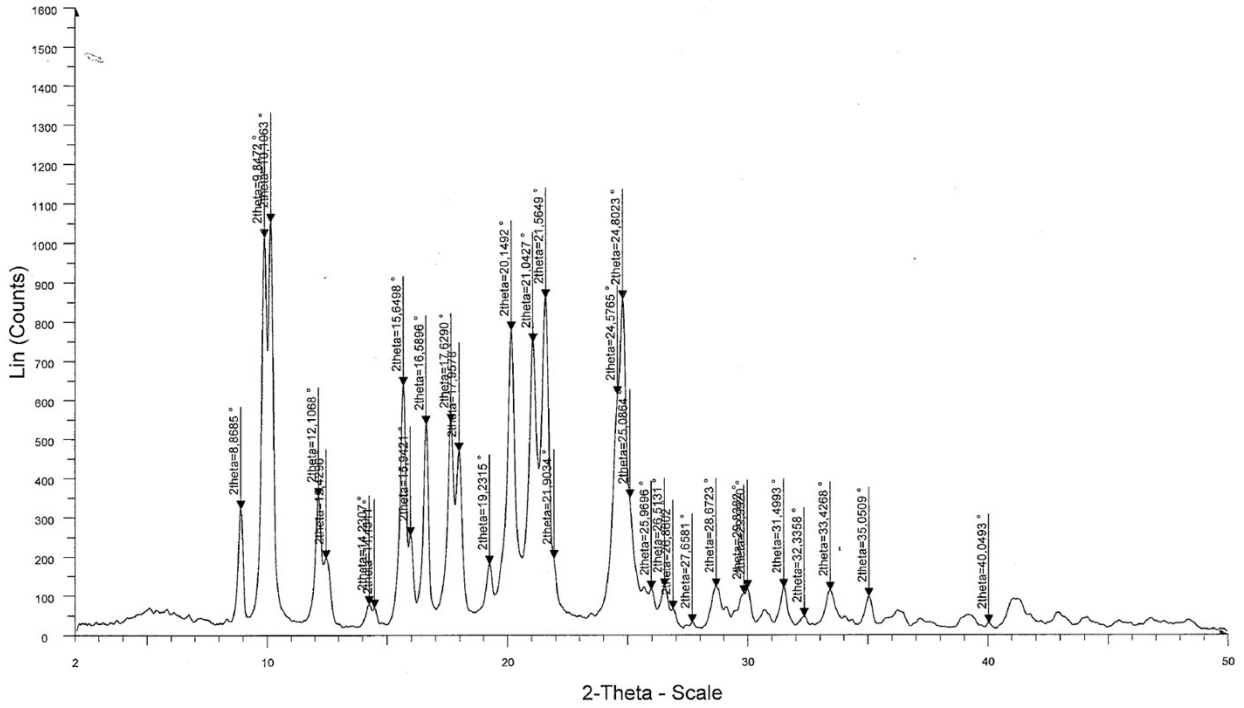


(a)

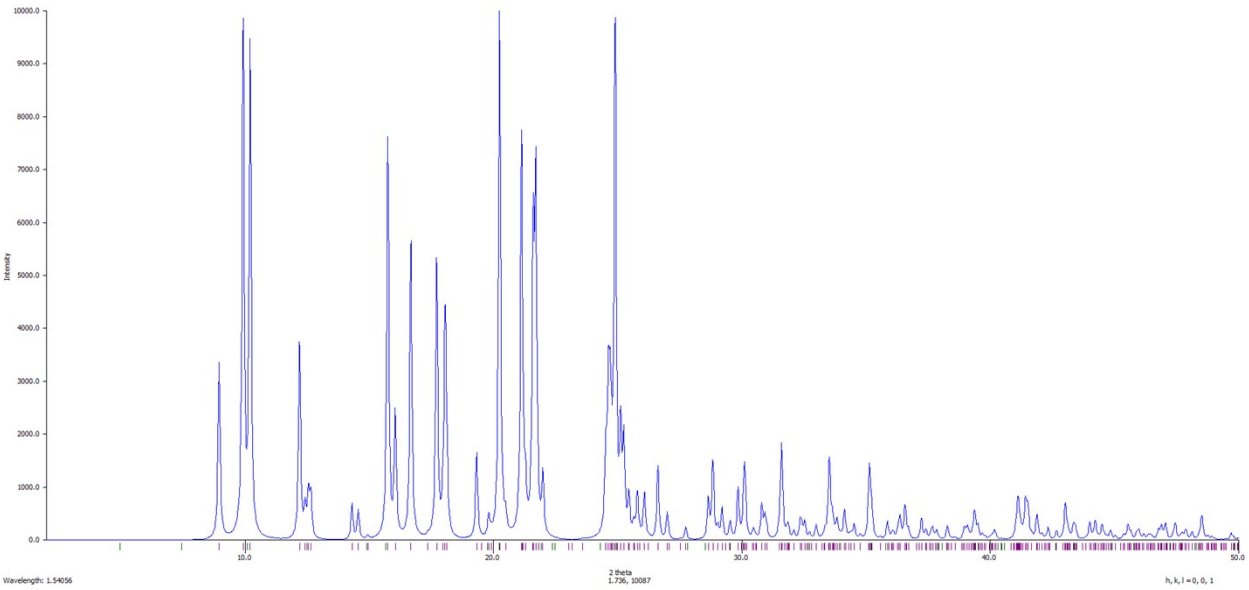


(b)

Figure S4. (a) Experimental PXRD pattern of TRS-FUM (1:1). (b) Simulated PXRD pattern of TRS FUM (1:1) generated from the crystal structure (image generated in CCDC Mercury 4.3.1 (Build 273970))

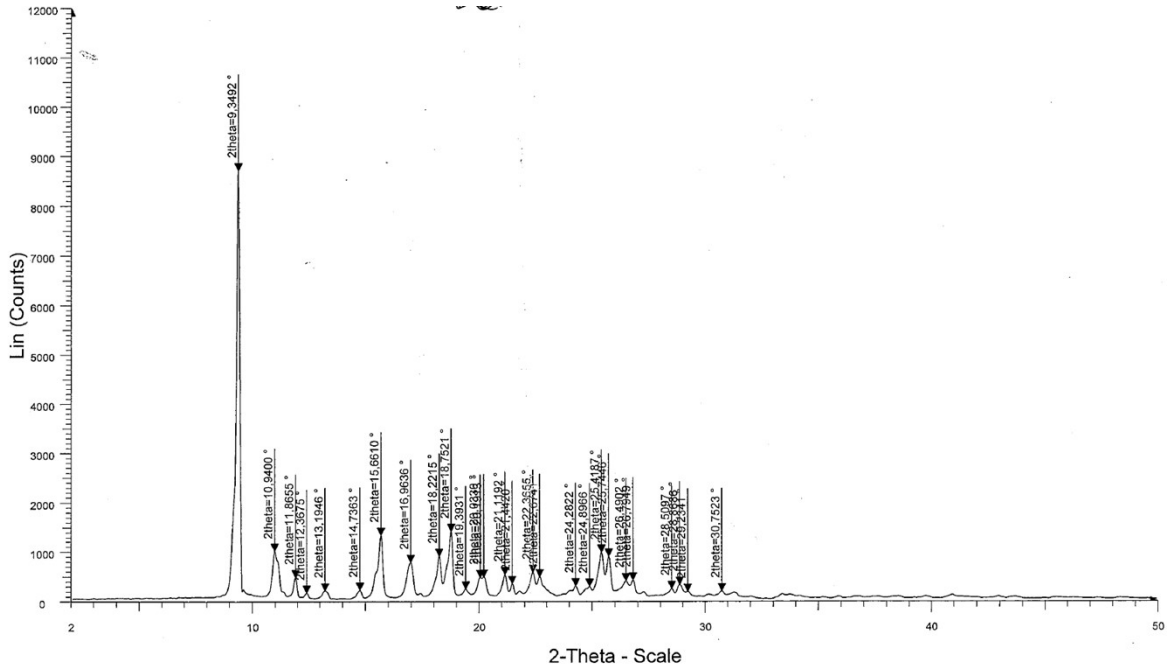


(a)

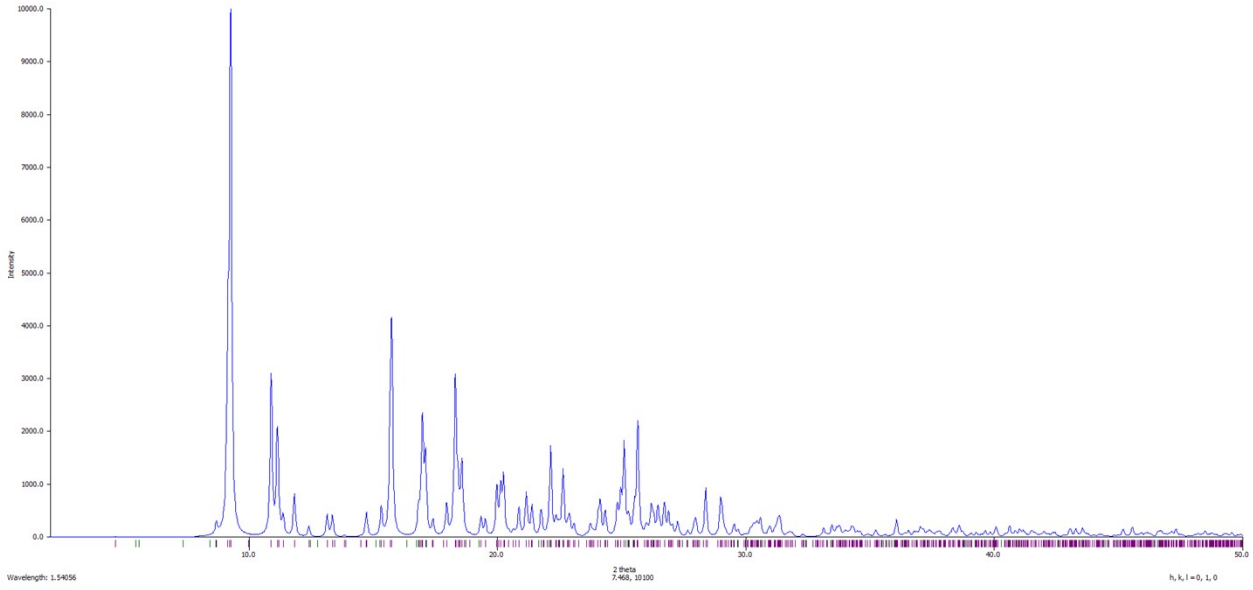


(b)

Figure S5. (a) Experimental PXRD pattern of TRS-OX (2:1). (b) Simulated PXRD pattern of TRS-OX (2:1) generated from the crystal structure (image generated in CCDC Mercury 4.3.1 (Build 273970))

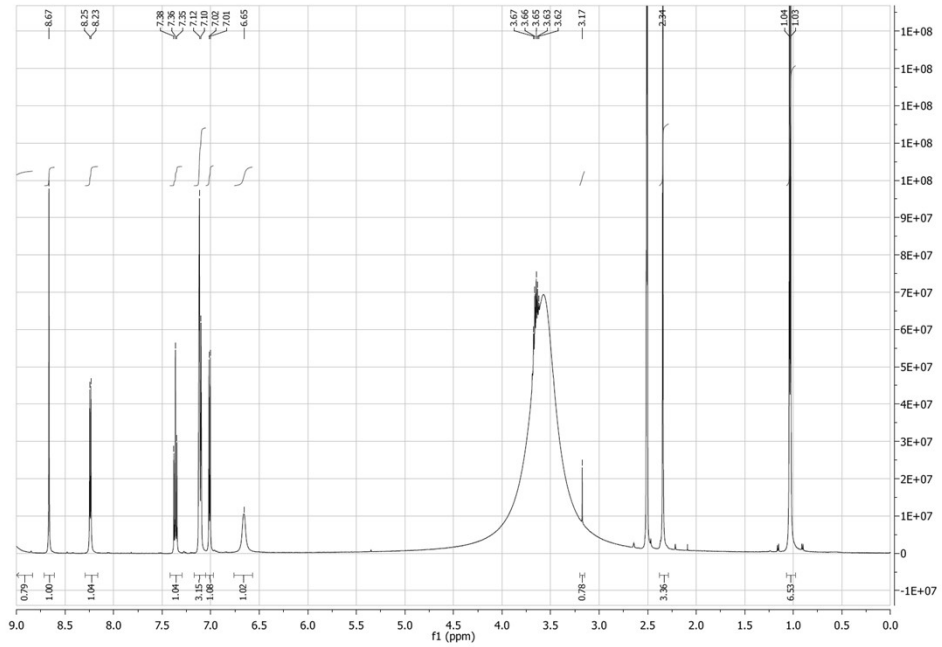


(a)

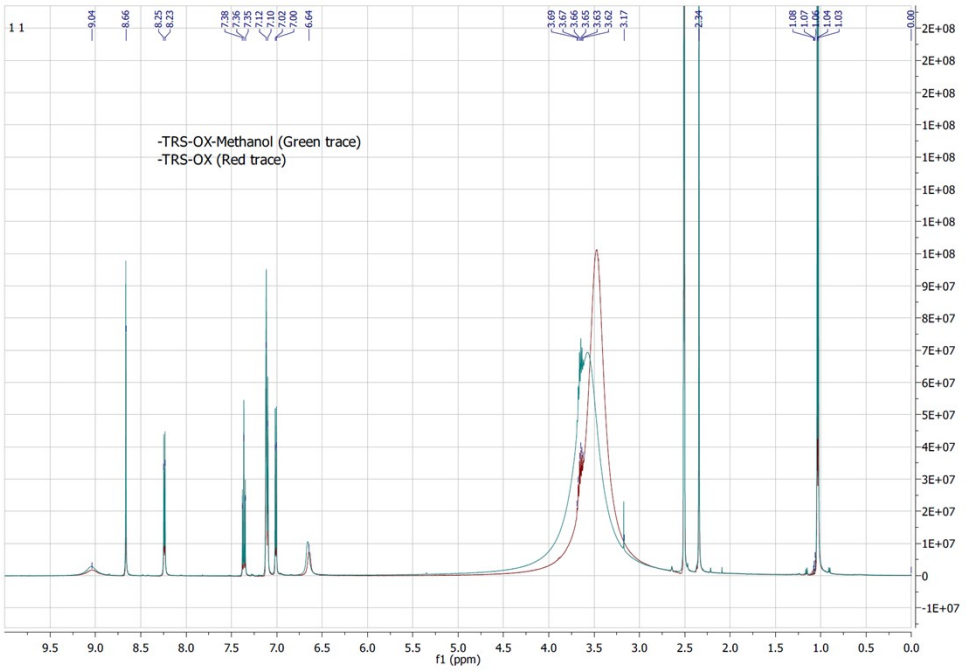


(b)

Figure S6. (a) Experimental PXRD pattern of TRS-OX-M (2:1:0.56). (b) Simulated PXRD pattern of TRS-OX-M (2:1:0.56) generated from the crystal structure (image generated in CCDC Mercury 4.3.1 (Build 273970))



(a)



(b)

Figure S7. (a) ^{1}H-NMR spectrum of TRS-OX-M material recorded in DMSO-d_6 showing the partial site occupancy of methanol solvent. (b) Comparison of ^{1}H-NMR spectrum of TRS-OX-M with the ^{1}H-NMR anhydrous TRS-OX. The extra peak at 3.17ppm corresponds to CH3 of Methanol.

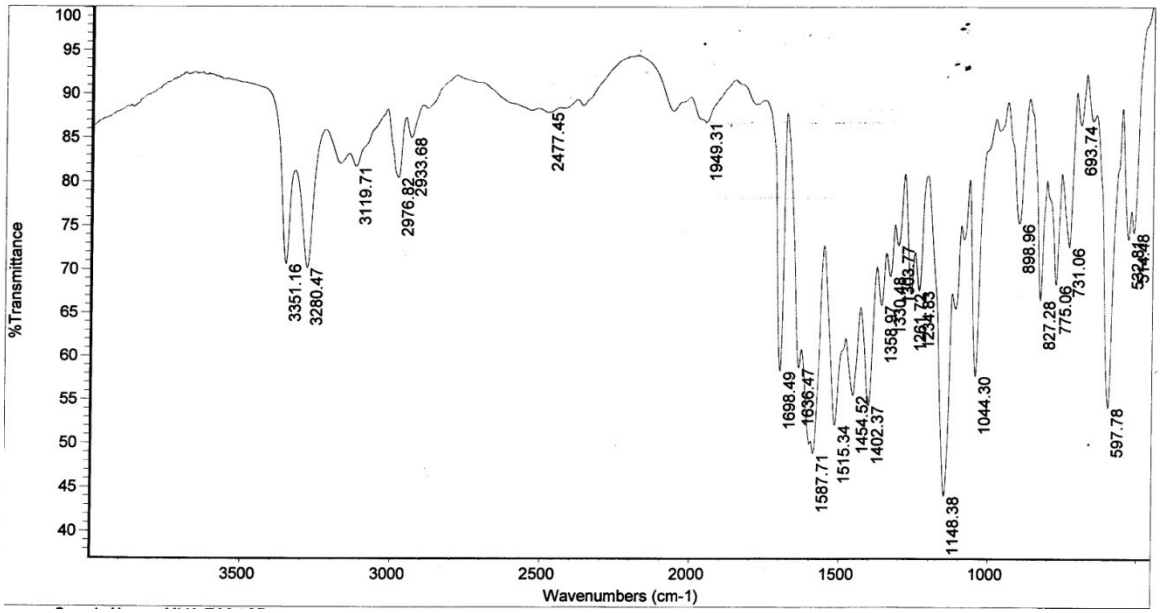


Figure S8. The FT-IR spectrum of polymorph T-I of torasemide.

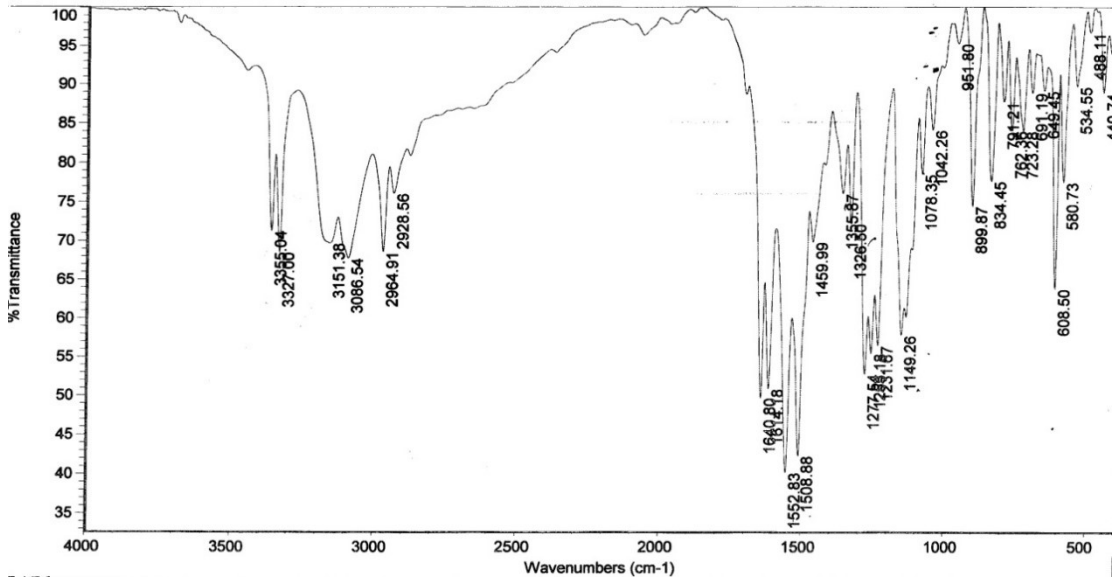


Figure S9. The FT-IR spectrum of polymorph T-III/T-N of torasemide.

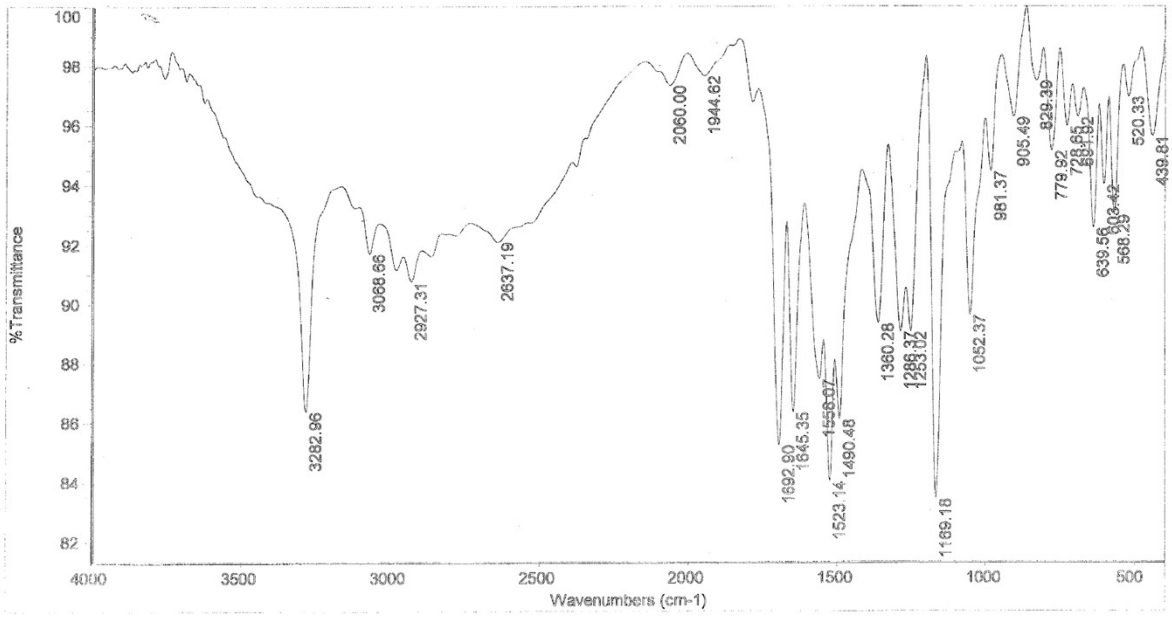


Figure S10. The FT-IR spectrum of torasemide fumarate (TRS-FUM) salt (1:1).

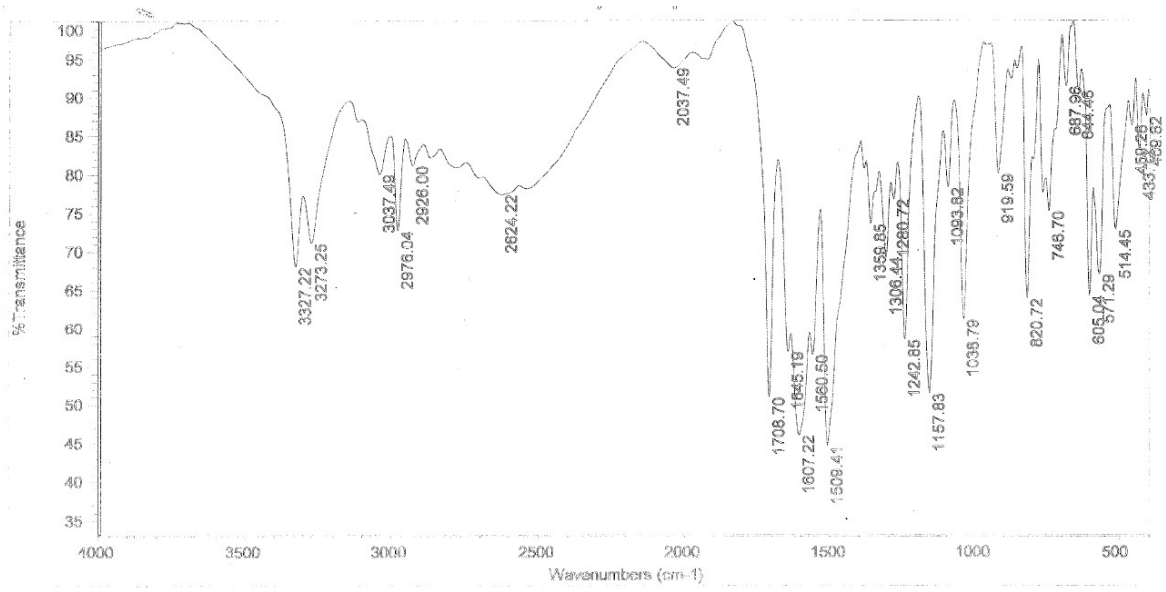


Figure S11. The FT-IR spectrum of torasemide oxalate (TRS-OX) salt (2:1).

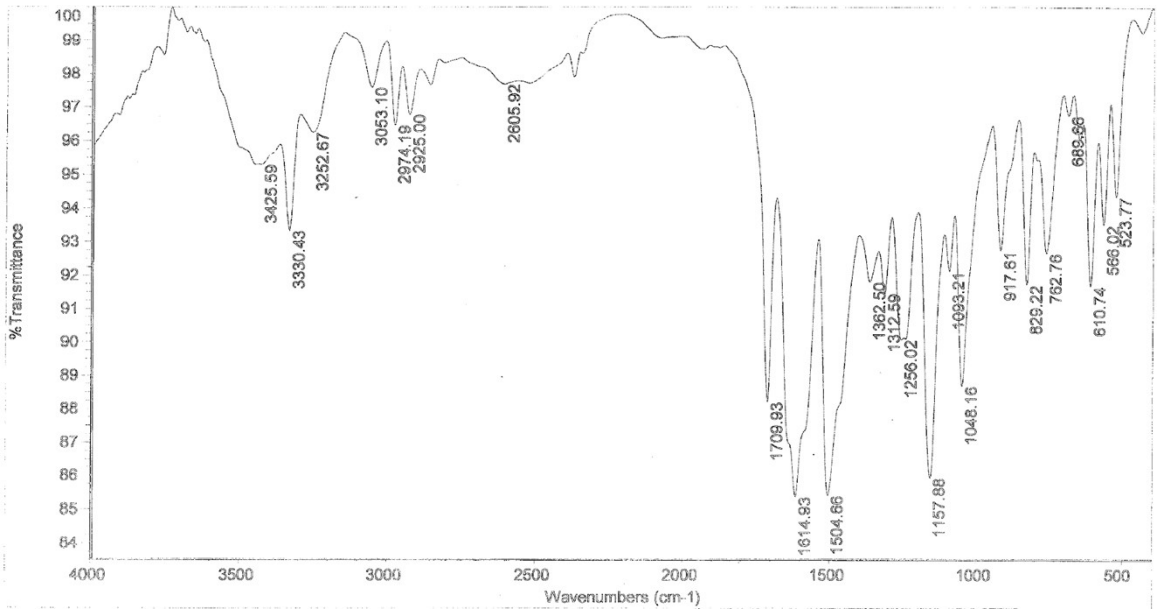


Figure S12. The FT-IR spectrum of torasemide oxalate methanolate salt (TRS-OX-M) (2:1:0.56).

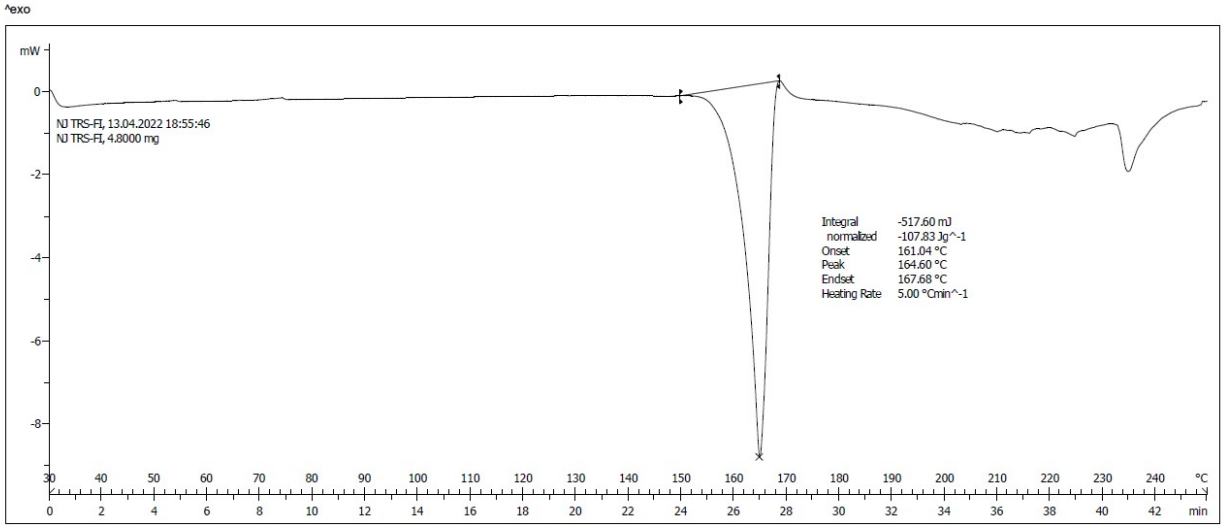


Figure S13. DSC thermogram of polymorph T-I of torasemide recorded at heating rate of 5°C/min from RT to 250°C. It shows a single melting endothermic event (T_{onset} at 161.0±0.2°C, T_{peak} at 164.6°C ±0.2°C, T_{endset} at 167.7±0.2°C, Heat of fusion value of 107.8±0.5 J/g).

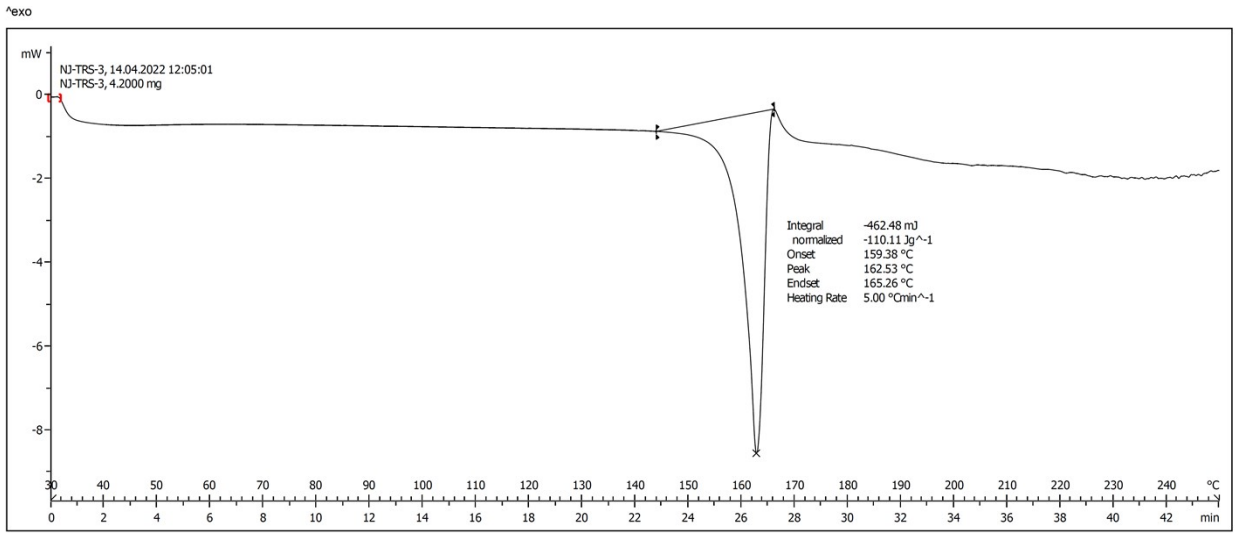


Figure S14. DSC thermogram of polymorph T-III/T-N of torasemide recorded at heating rate of 5°C/min from RT to 250°C. It shows a single melting endothermic event (T_{onset} at 159.3±0.2°C, T_{peak} at 162.5°C ±0.2°C, T_{endset} at 165.2±0.2°C, Heat of fusion value of 110.1±0.5 J/g).

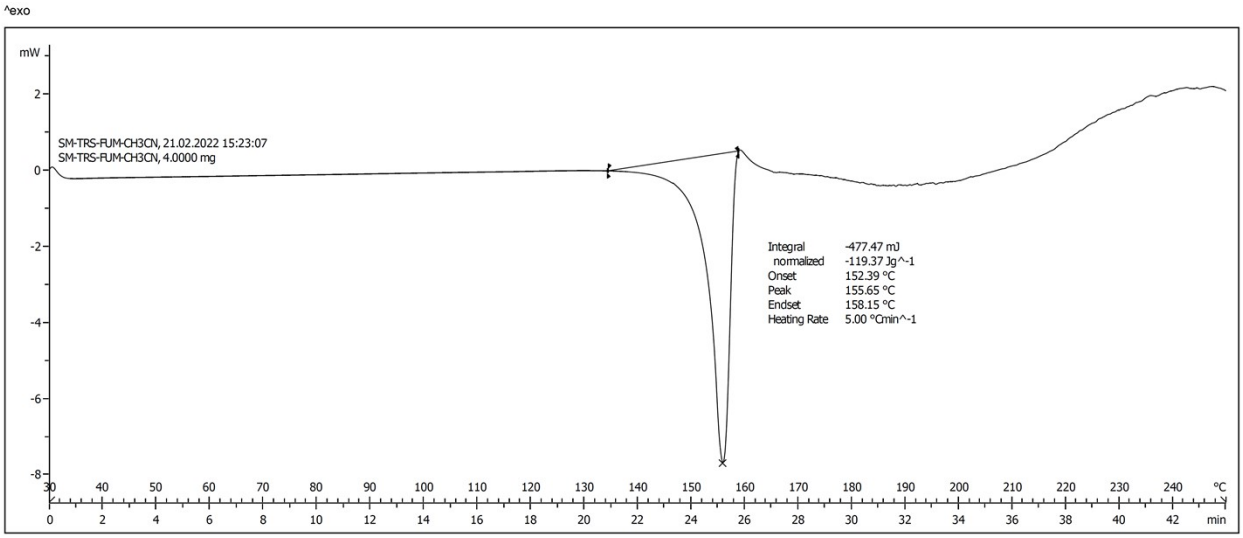


Figure S15. DSC thermogram of torasemide fumarate (TRS-FUM) salt (1:1) recorded at heating rate of 5°C/min from RT to 250°C. It shows a single melting endothermic event (T_{onset} at 152.3±0.2°C, T_{peak} at 155.6°C ±0.2°C, T_{endset} at 158.1±0.2°C, Heat of fusion value of 119.3±0.5 J/g).

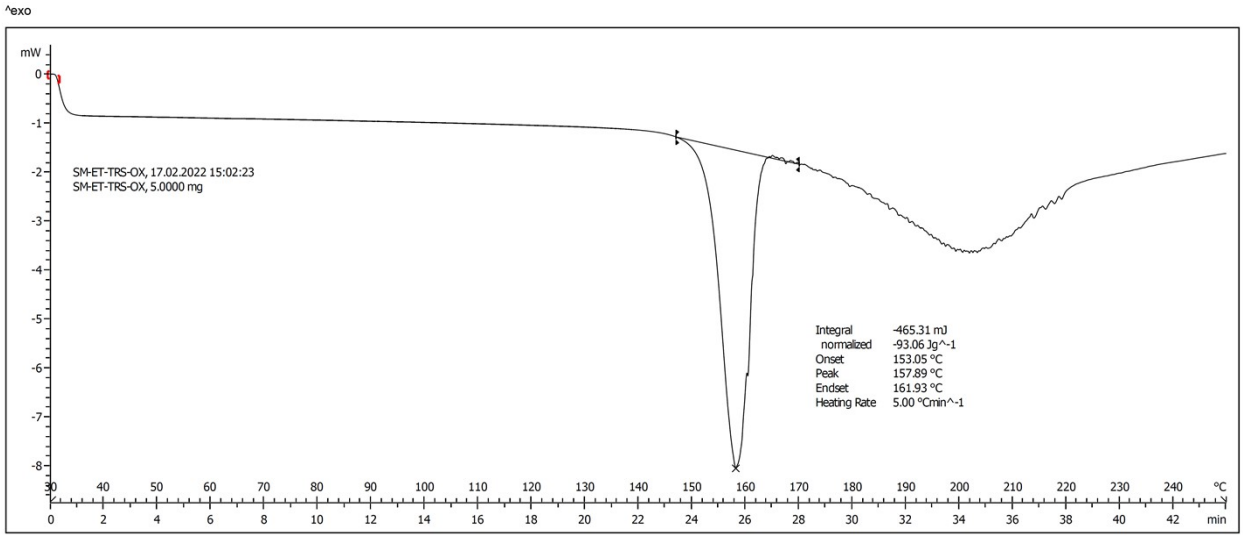


Figure S16. DSC thermogram of torasemide oxalate (TRS-OX) salt (2:1) recorded at heating rate of 5°C/min from RT to 250°C. It shows a single melting endothermic event (T_{onset} at 153.0±0.2°C, T_{peak} at 157.8°C ±0.2°C, T_{endset} at 161.9±0.2°C, Heat of fusion value of 93.0±0.5 J/g).

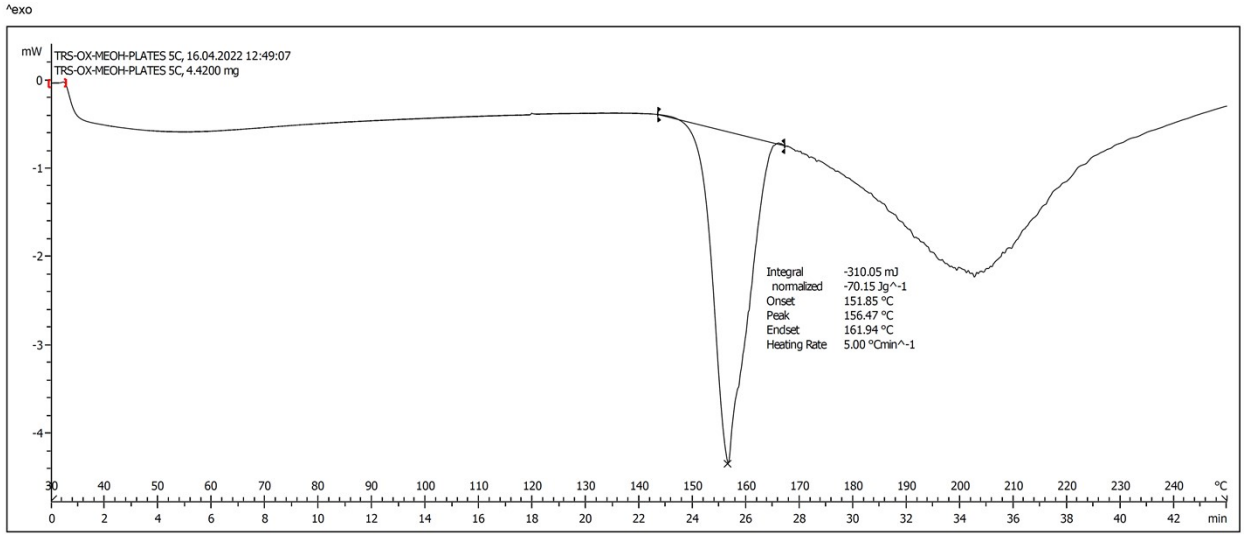


Figure S17. DSC thermogram of torasemide oxalate methanolate (TRS-OX-M) salt (2:1:0.56) recorded at heating rate of 5°C/min from RT to 250°C. It shows a single melting endothermic event (T_{onset} at 151.8±0.2°C, T_{peak} at 156.4°C ±0.2°C, T_{endset} at 161.9±0.2°C, Heat of fusion value of 70.1±0.5 J/g).

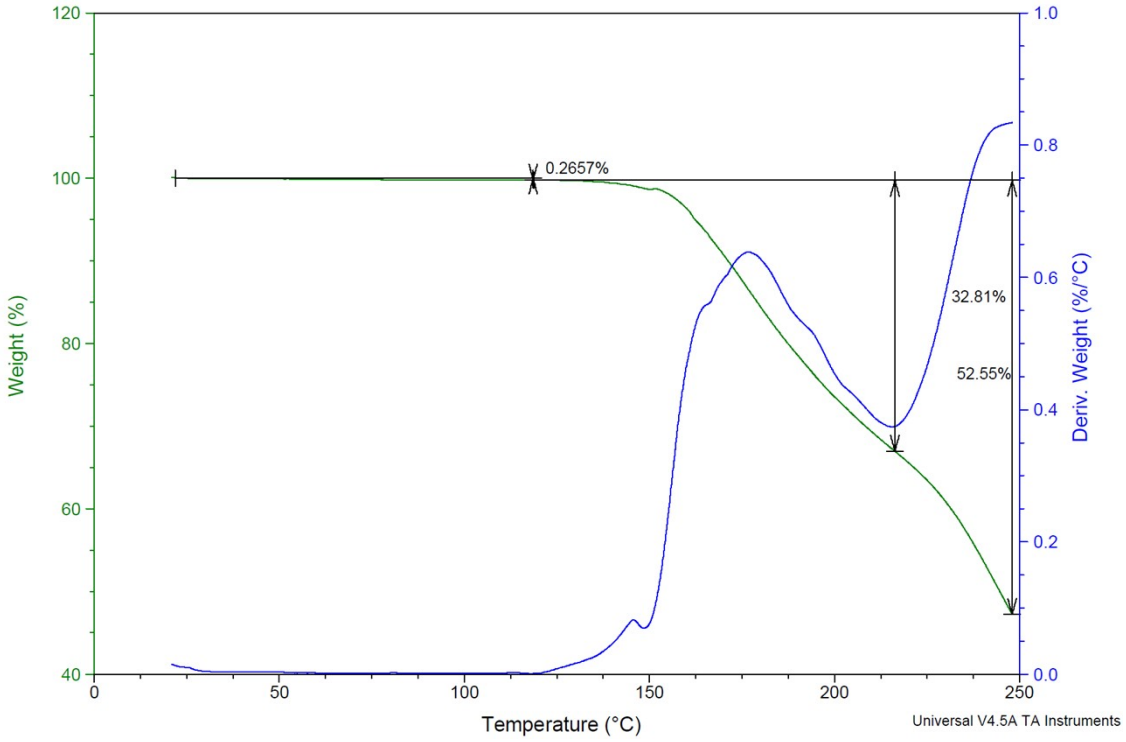


Figure S18. TGA plot of torasemide oxalate (TRS-FUM) salt (2:1) recorded at heating rate of 5°C/min from RT to 250°C. It shows a weight loss of 0.26% from RT to 100°C.

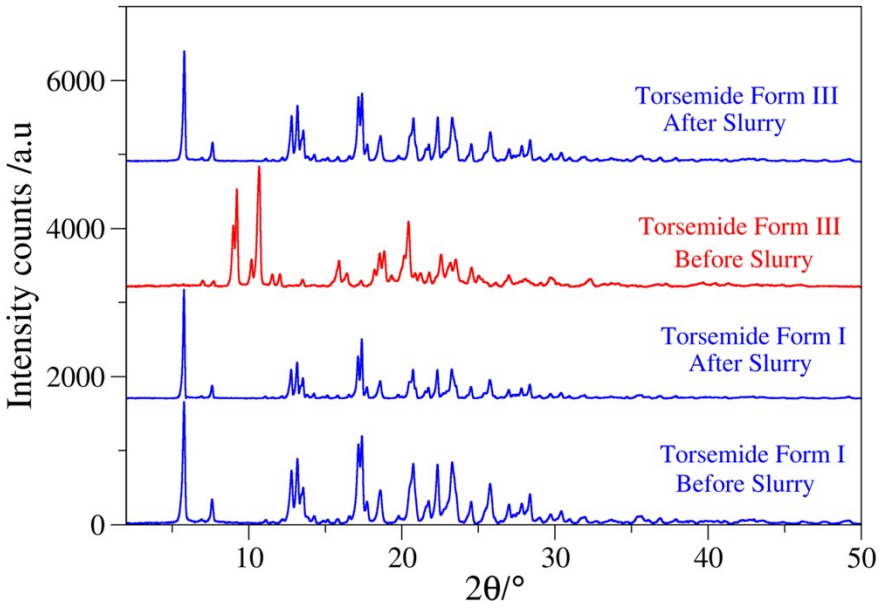


Figure S19. Slurry experiments of Torasemide in water. Torasemide form I remained stable after 24 hours of slurry, while Torasemide T-III/T-N converted to Torasemide form I, as indicated by changes in the powder X-ray diffraction pattern.

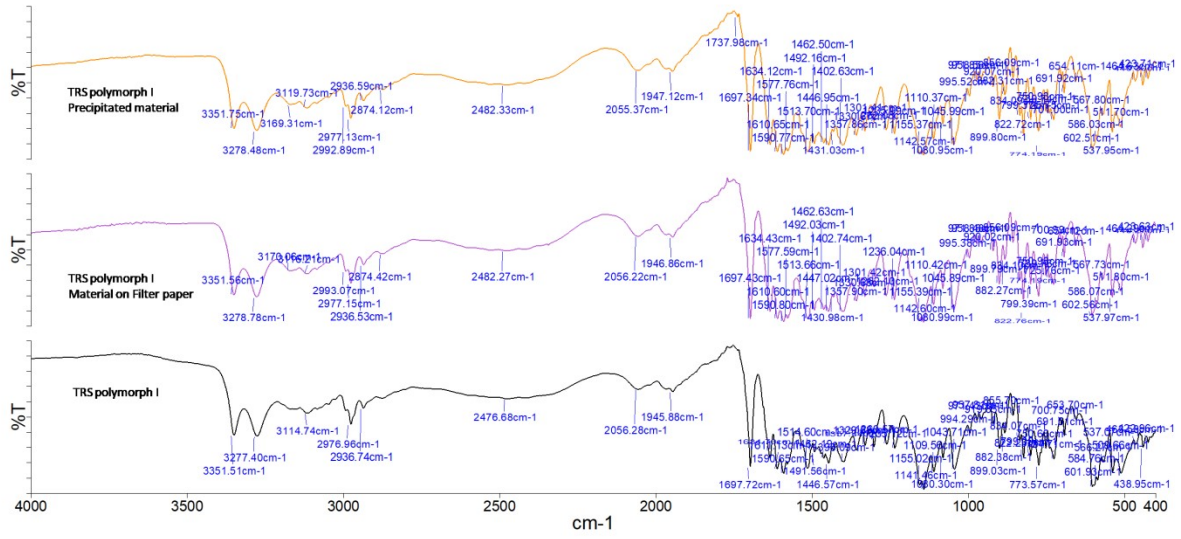


Figure S20. Slurry experiments of torasemide in water. Torasemide Form I remained stable after 24 hours of slurry.

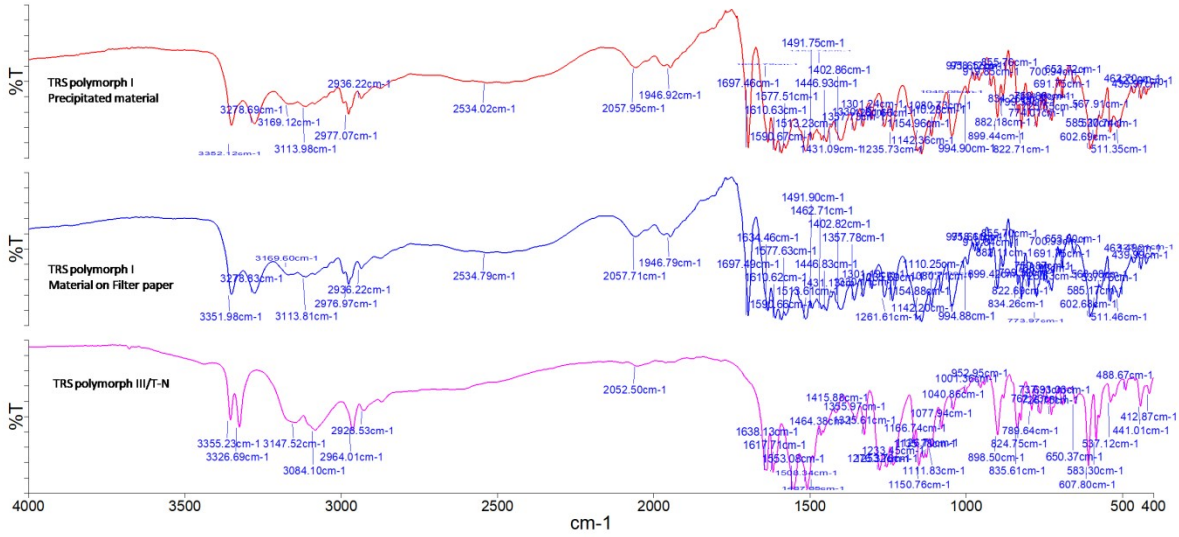


Figure S21. Slurry experiments of torasemide in water. Torasemide form III/T-N transformed to T-I after 24 hours of slurry.

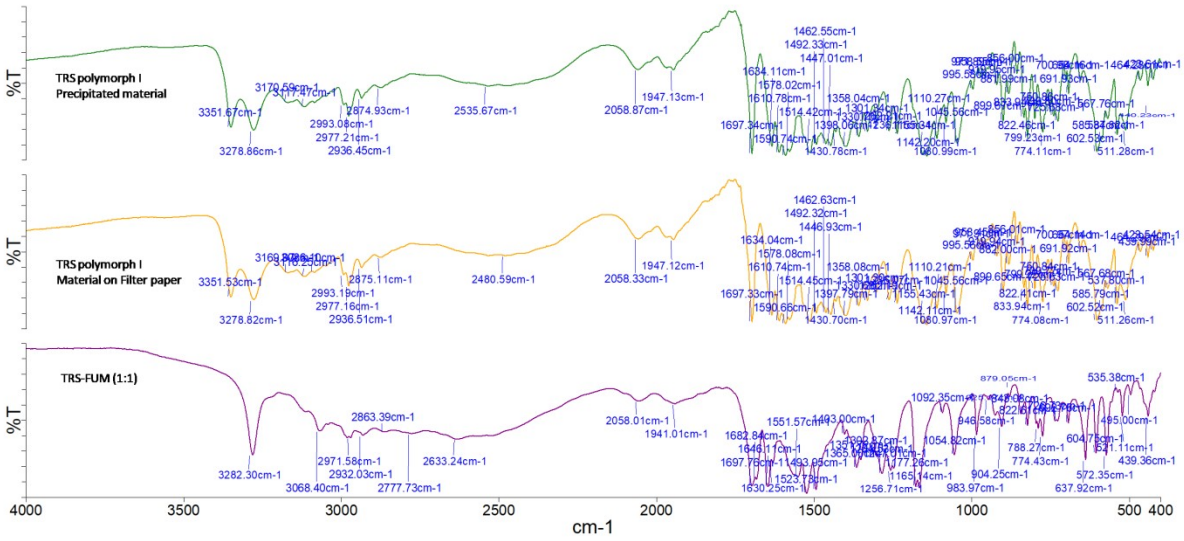


Figure S22. Slurry experiments of torasemide fumarate (1:1) salt in water which transformed to T-I polymorph of torasemide.

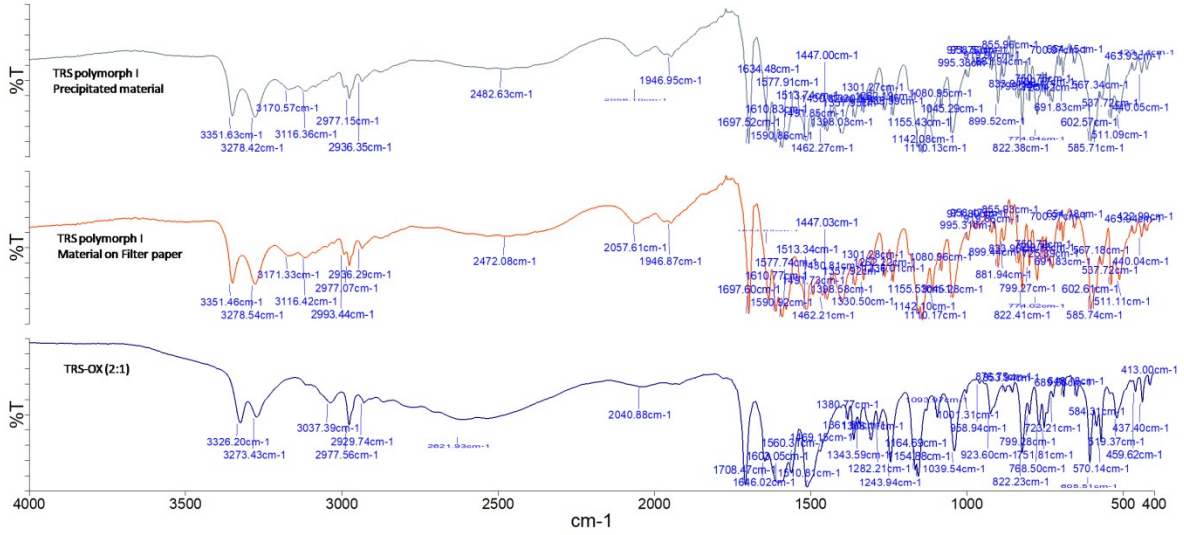


Figure S23. Slurry experiments of torasemide oxalate (2:1) salt in water which transformed to T-I polymorph of torasemide.