

## Supporting Information

### **Rivaroxaban Eutectics with Improved Solubility, Dissolution Rate, Bioavailability and Stability**

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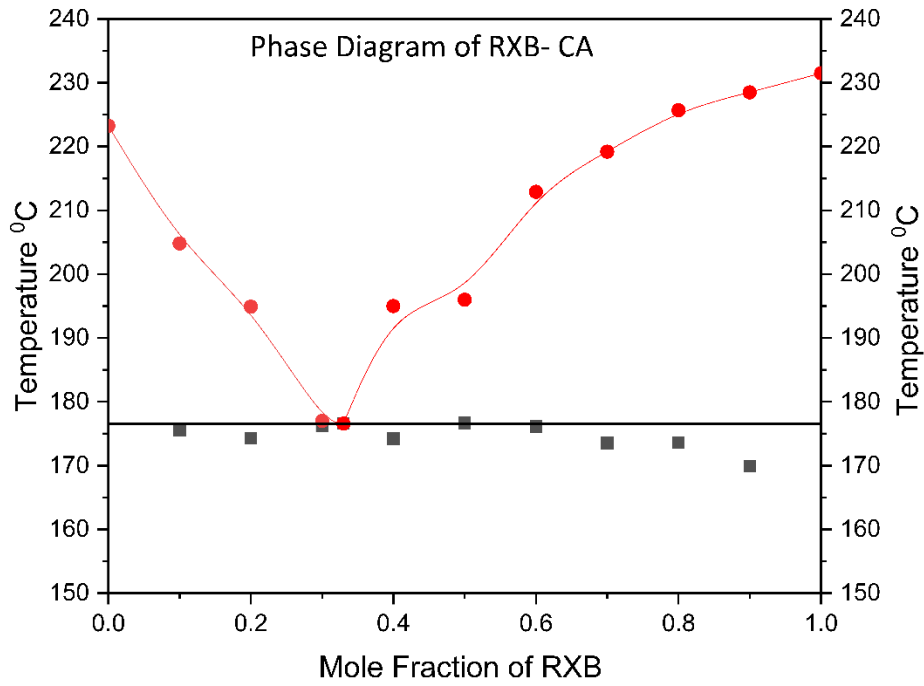
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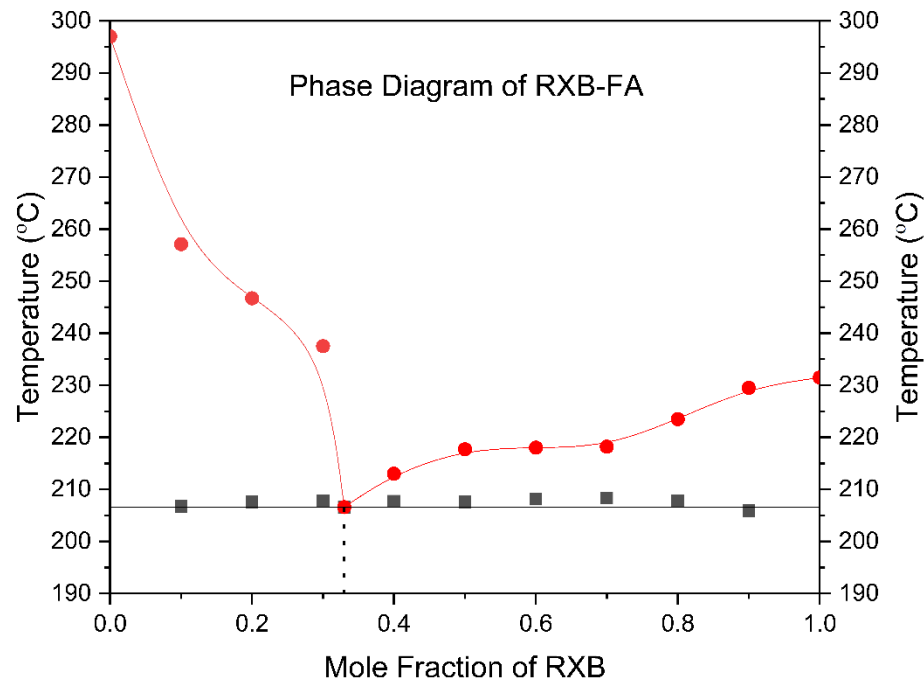
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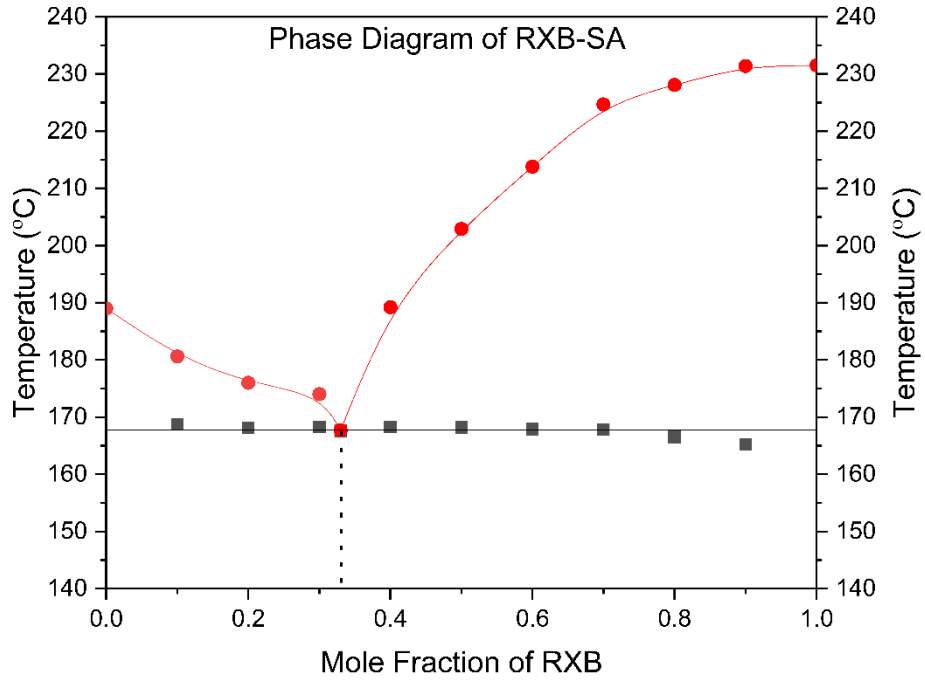
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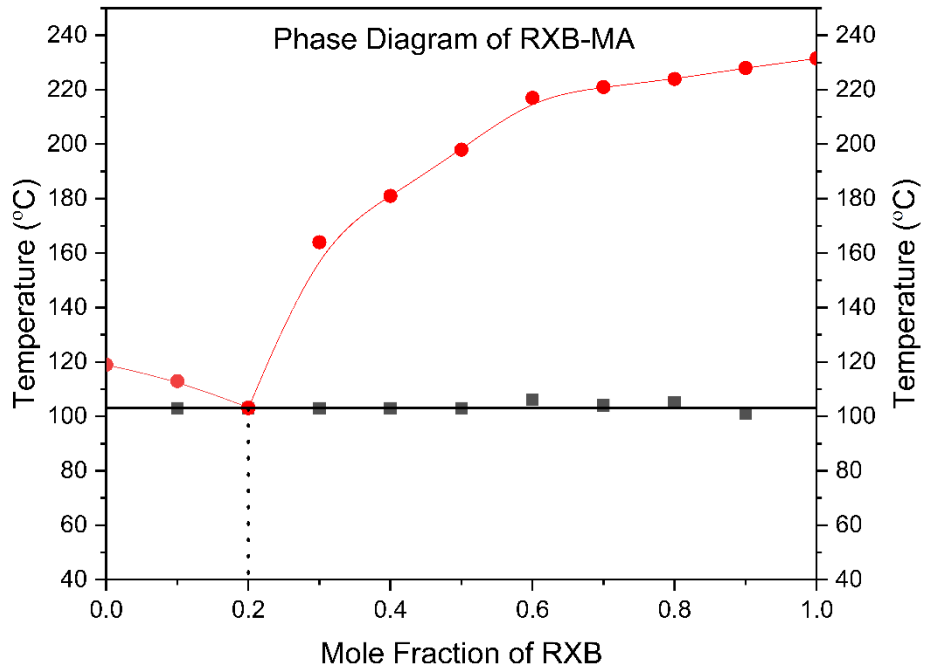
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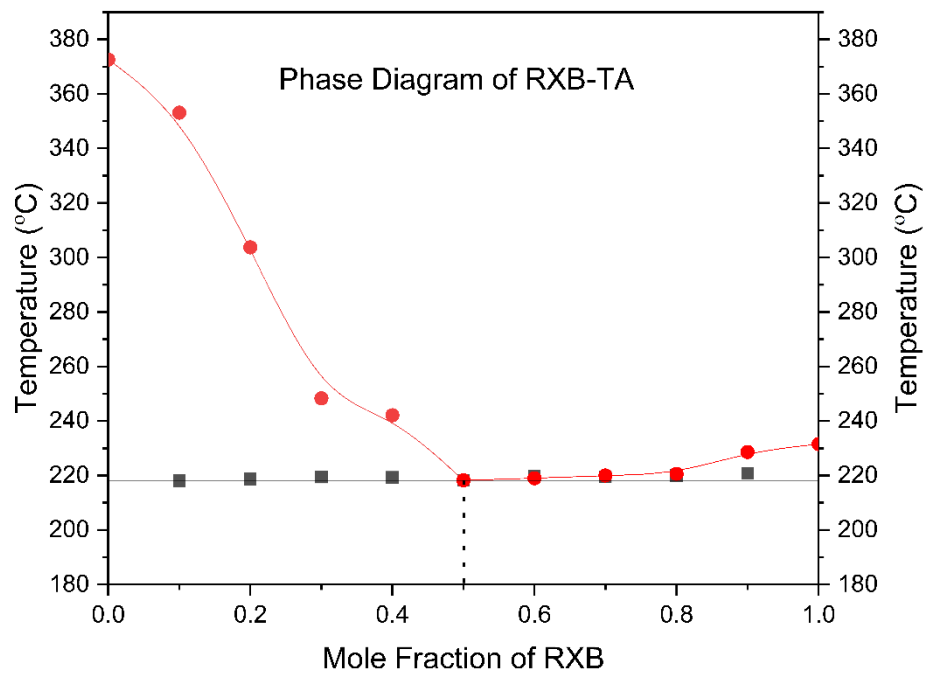
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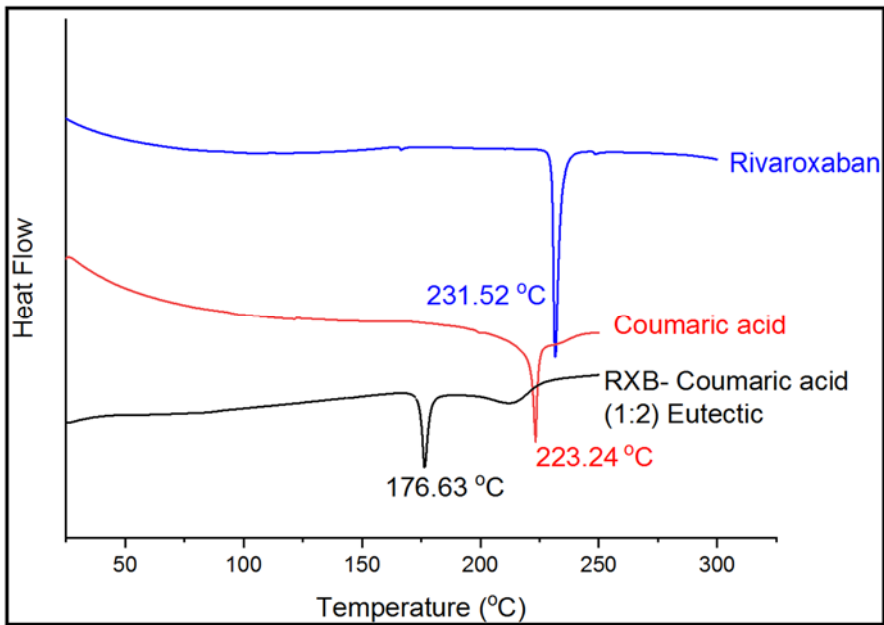


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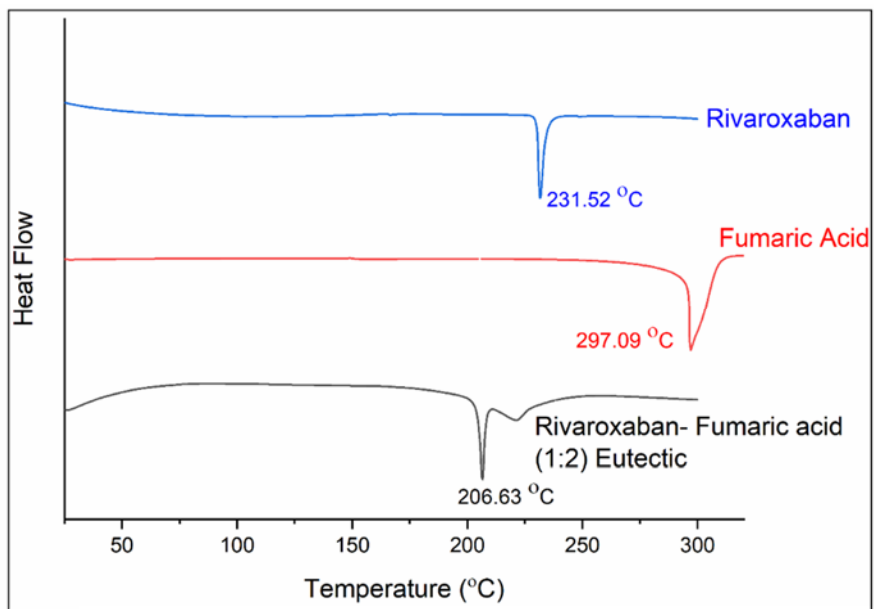


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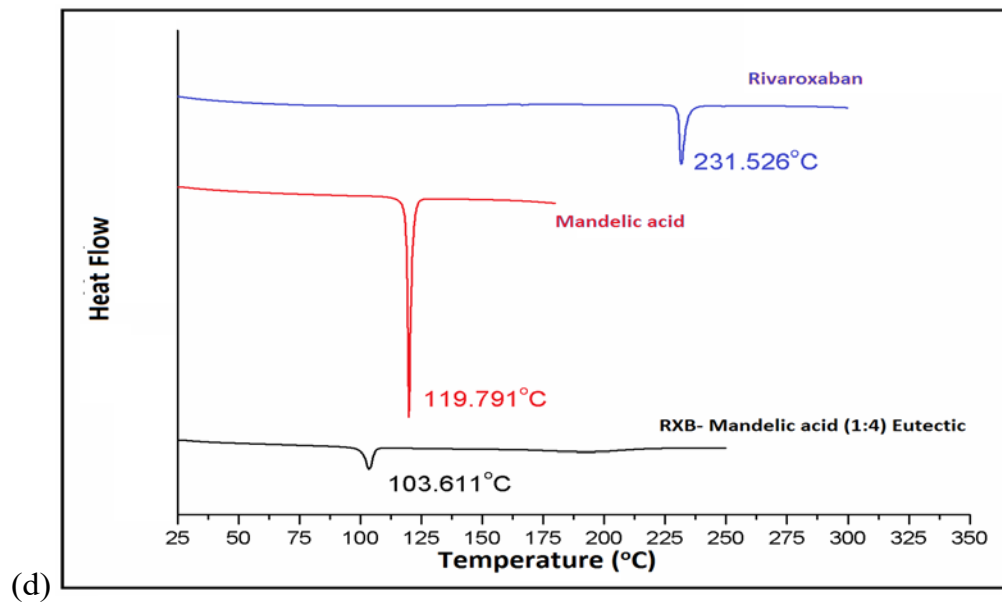
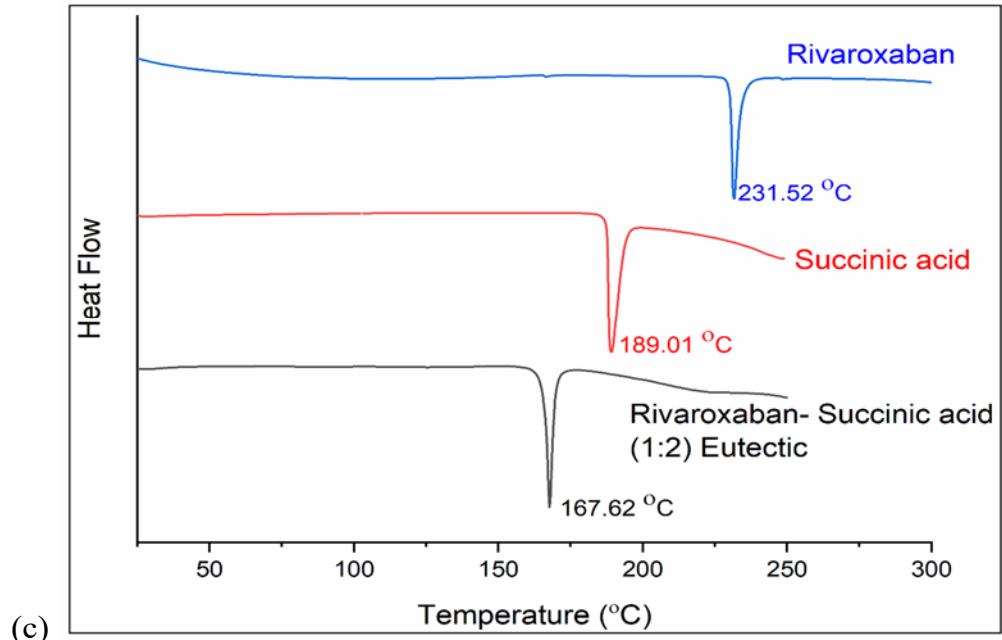
**Figure S1.** Binary Phase diagrams of eutectics, (a) RXB-CA, (b) RXB-FA, (c) RXB-SA, (d) RXB-MA and (e) RXB-TA.

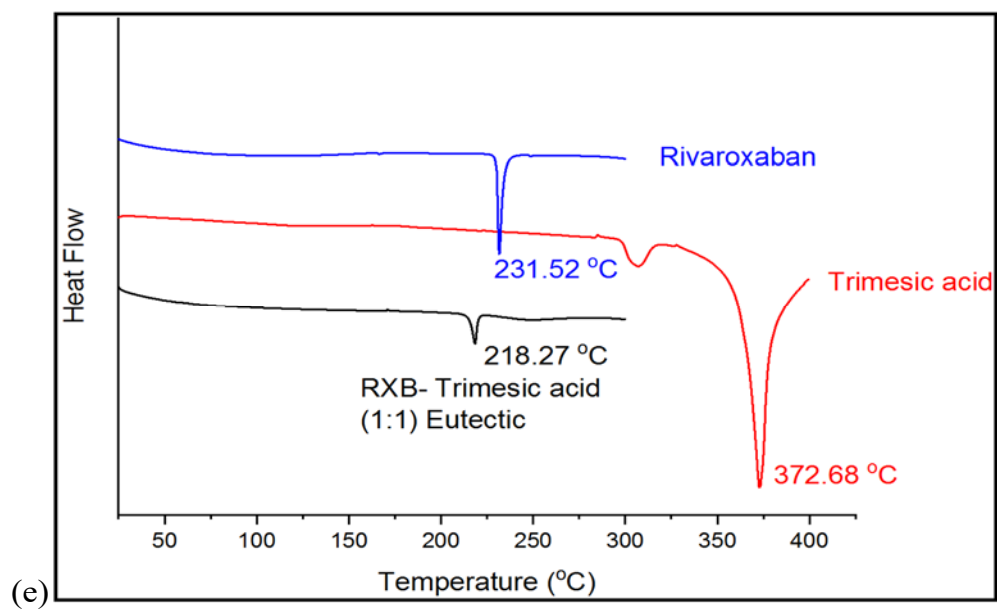


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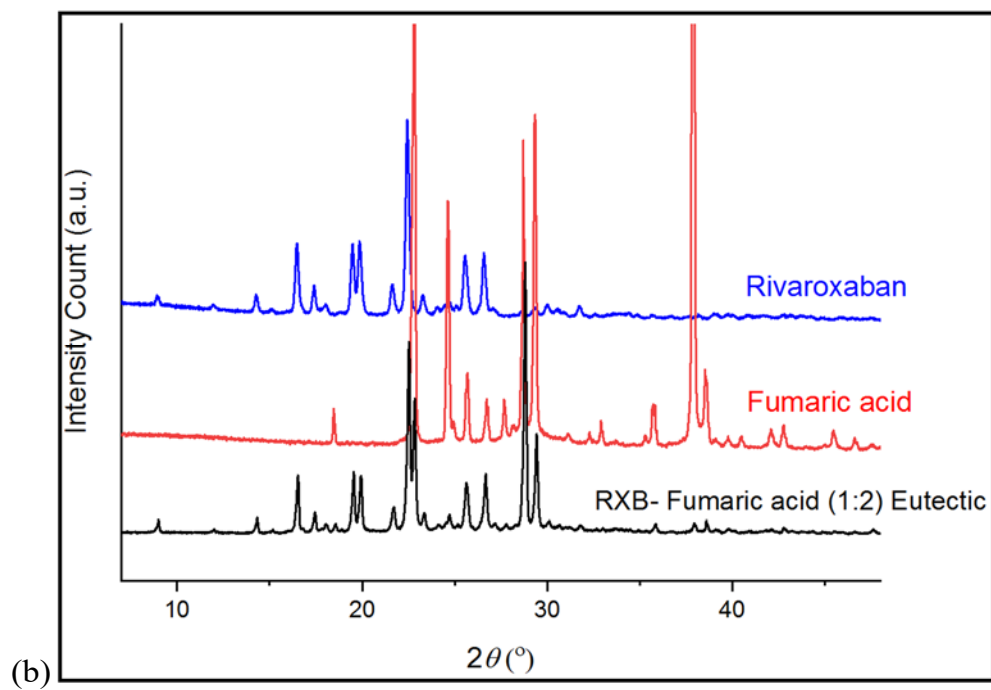
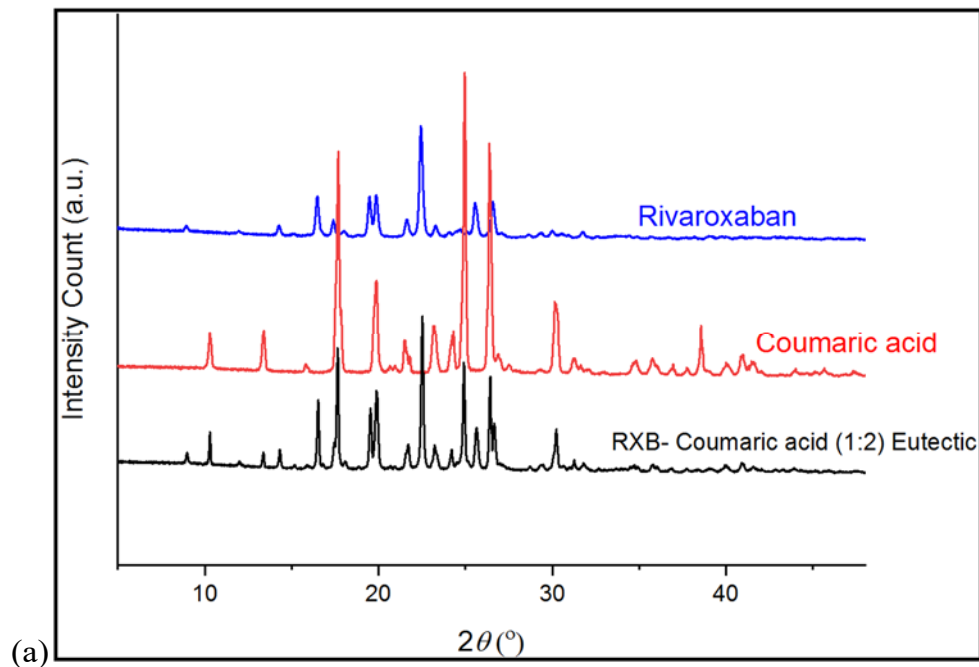
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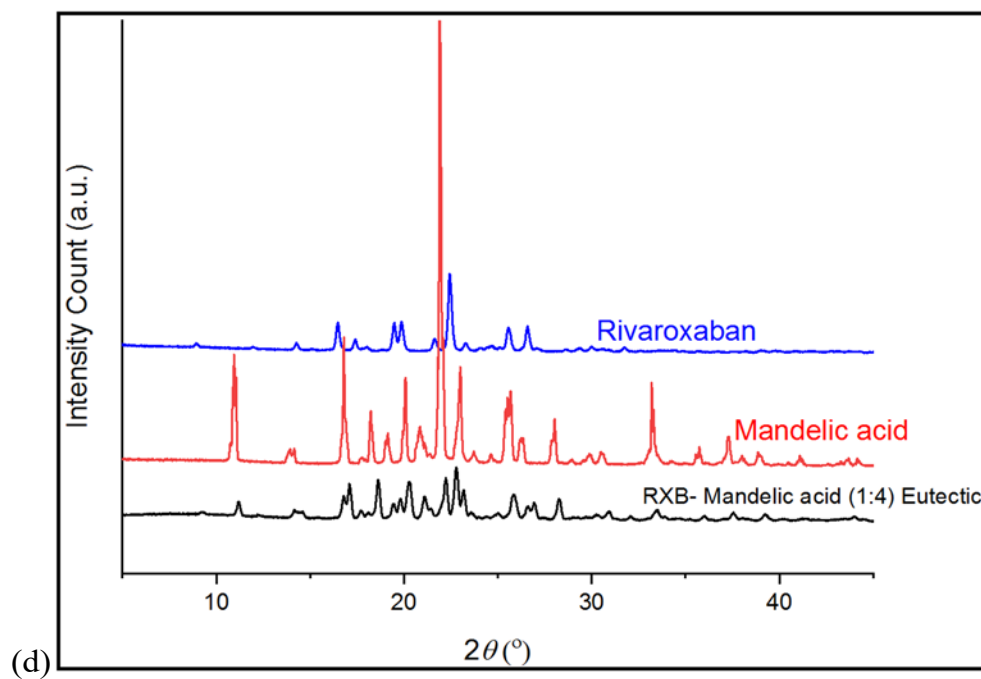
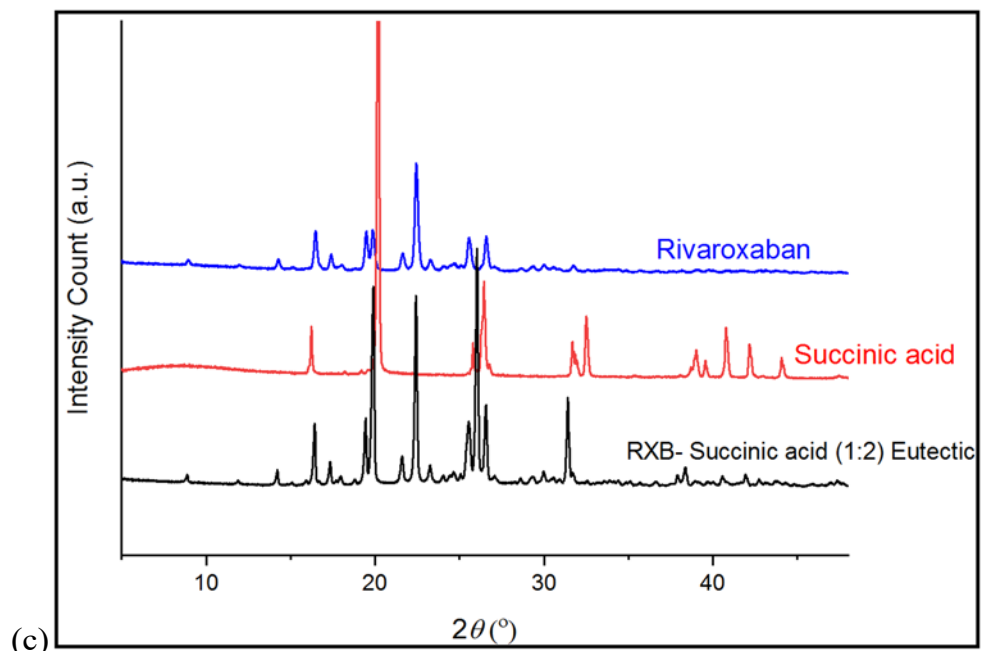


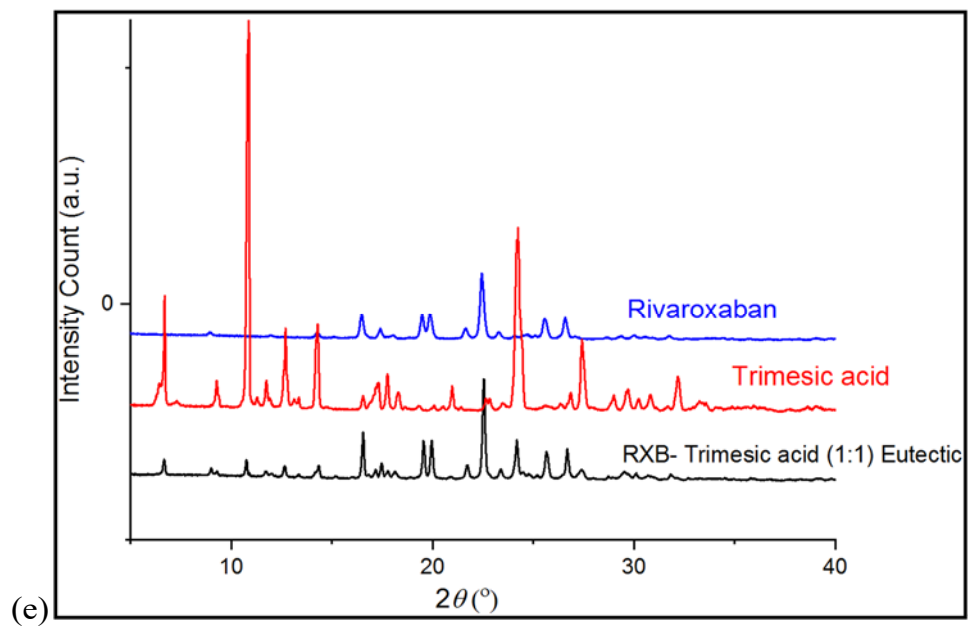


**Figure S2.** DSC thermograms of eutectics, (a) RXB, CA, RXB-CA (1:2), (b) RXB, FA, RXB-FA (1:2), (c) RXB, SA, RXB-SA (1:2), (d) RXB, MA, RXB-MA (1:4) and (e) RXB, TA, RXB-TA (1:1).

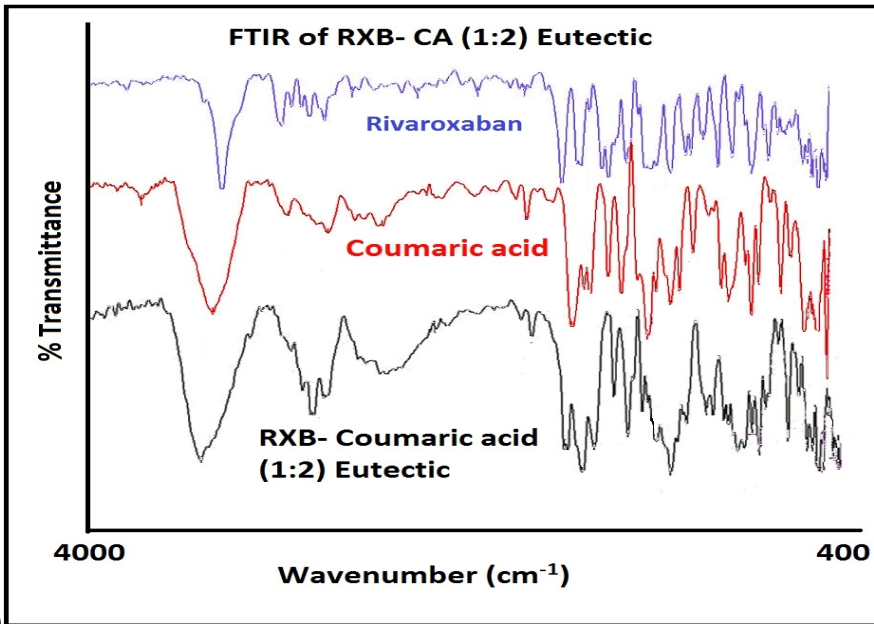




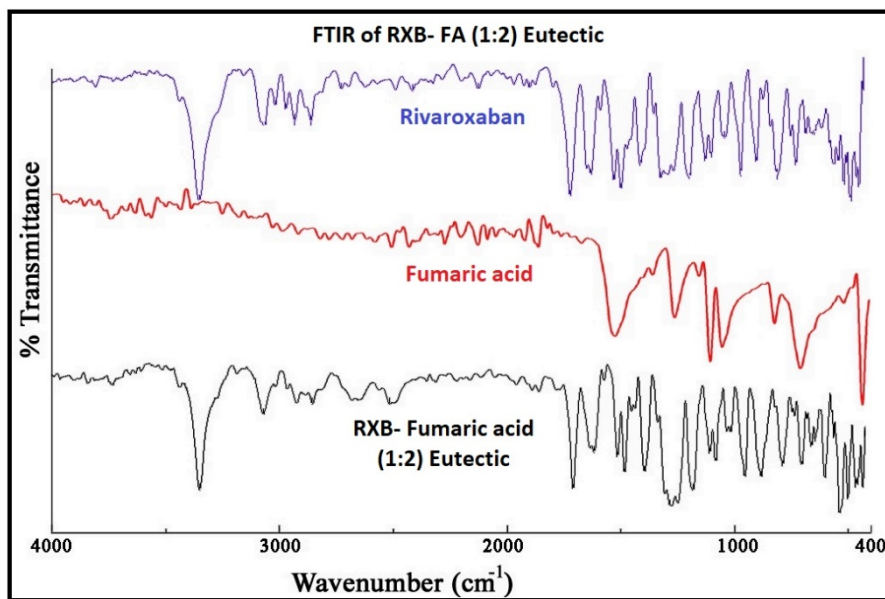




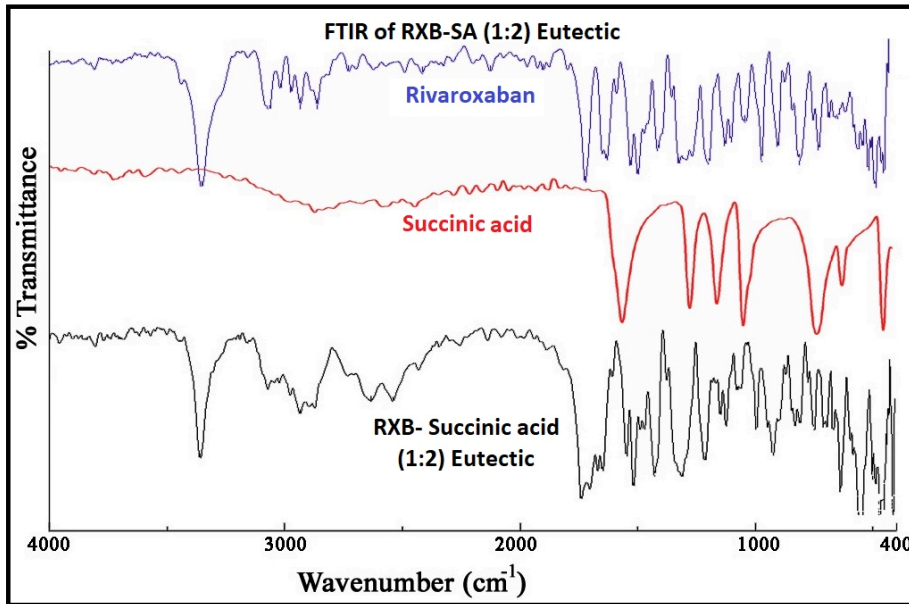
(e) **Figure S3.** PXRD profiles of eutectics, (a) RXB, CA, RXB-CA (1:2), (b) RXB, FA, RXB-FA (1:2), (c) RXB, SA, RXB-SA (1:2), (d) RXB, MA, RXB-MA (1:4) and (e) RXB, TA, RXB-TA (1:1).



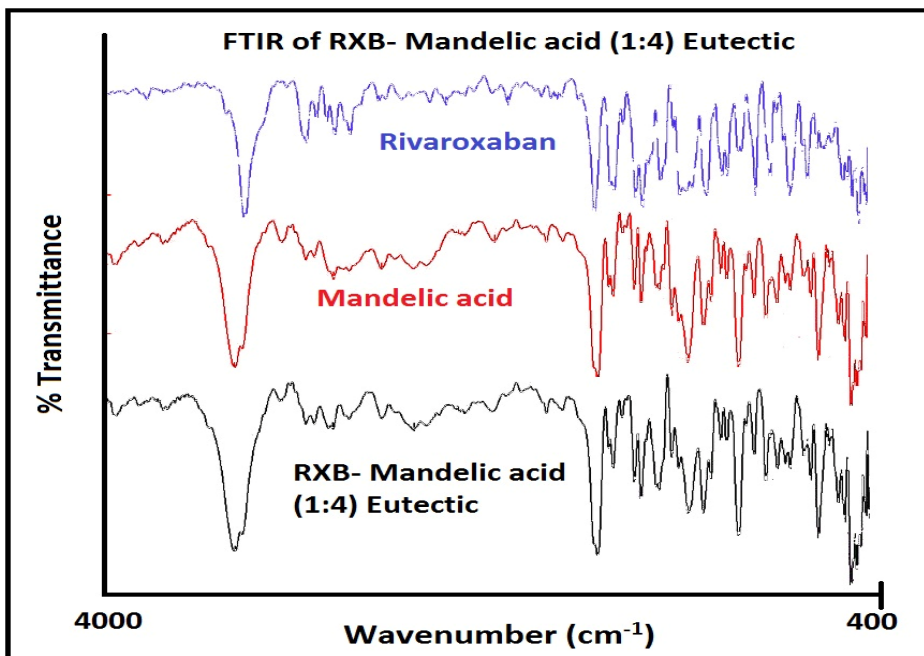
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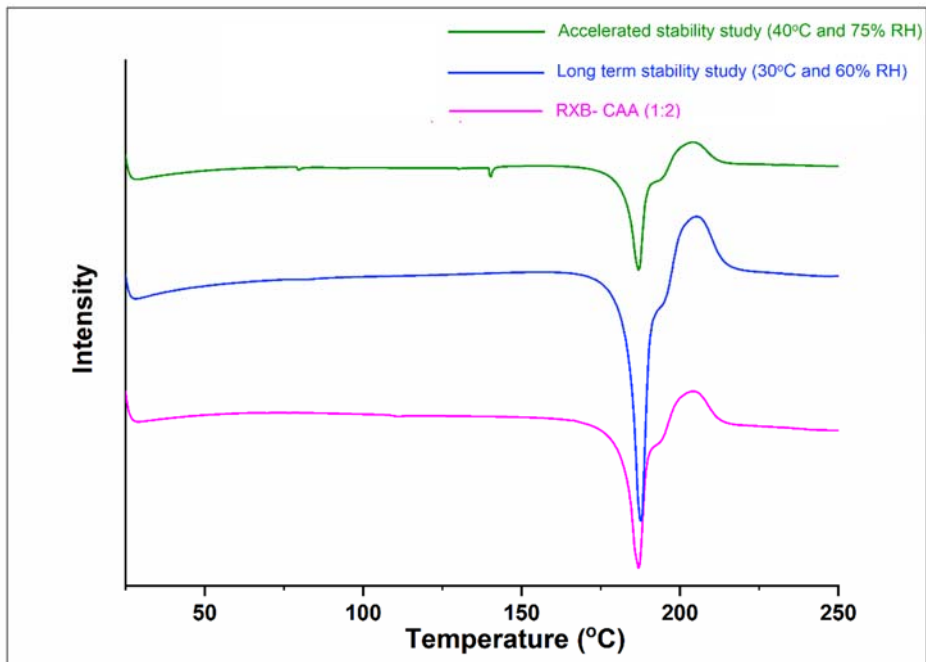


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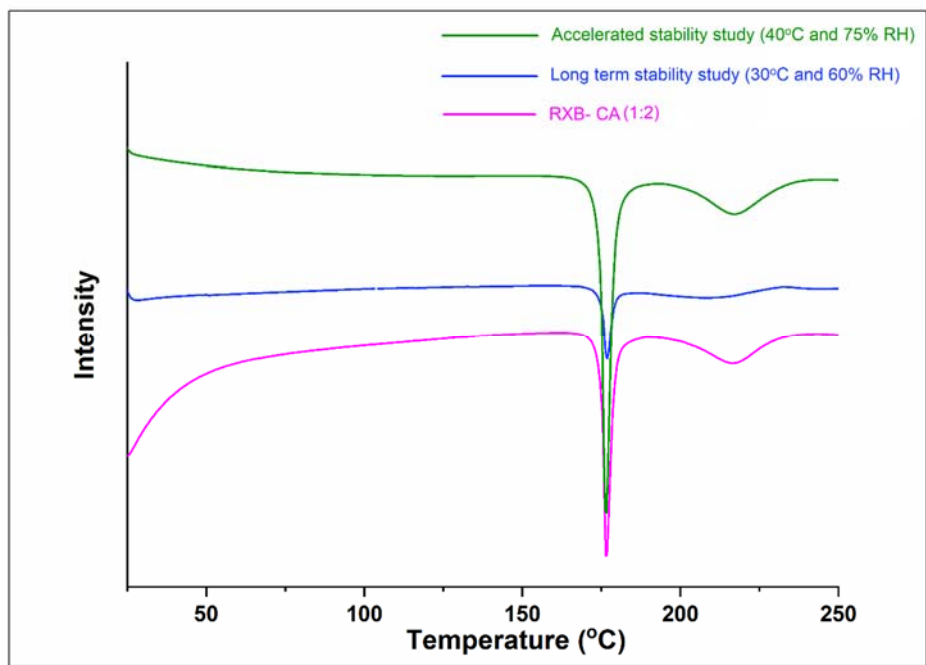


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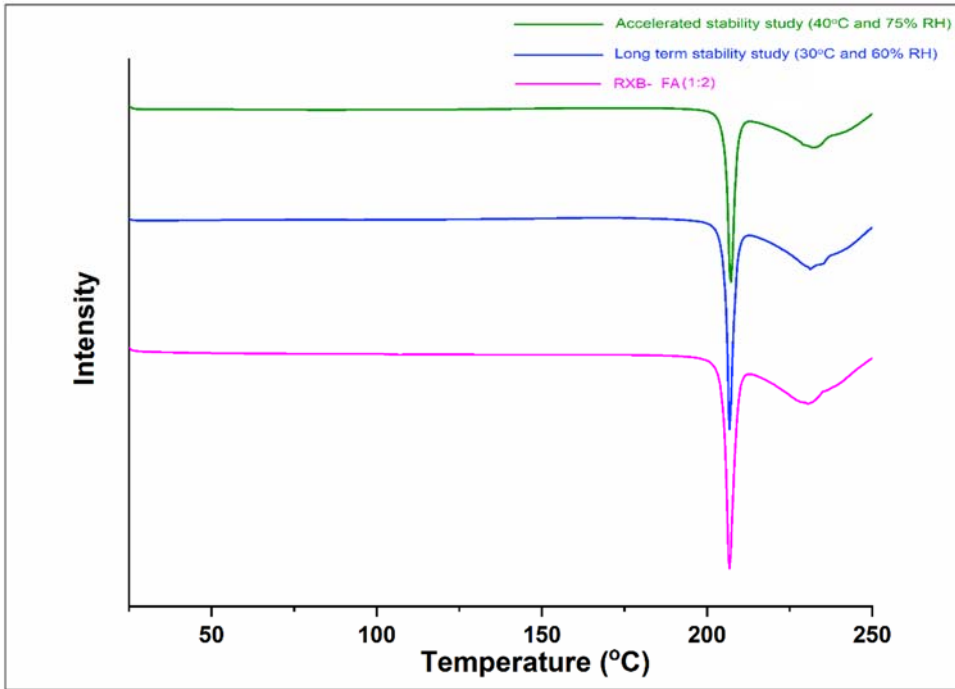




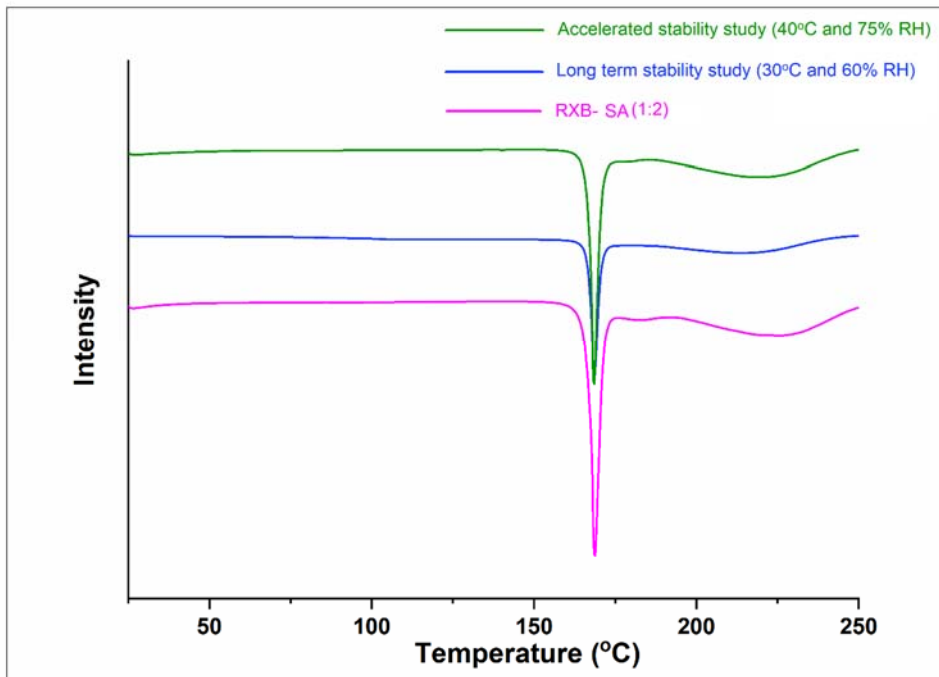
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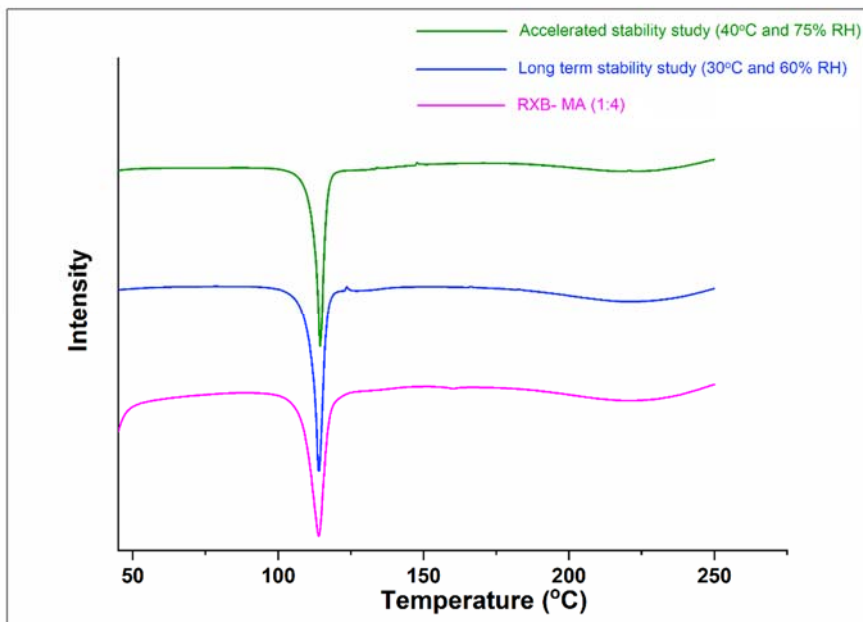


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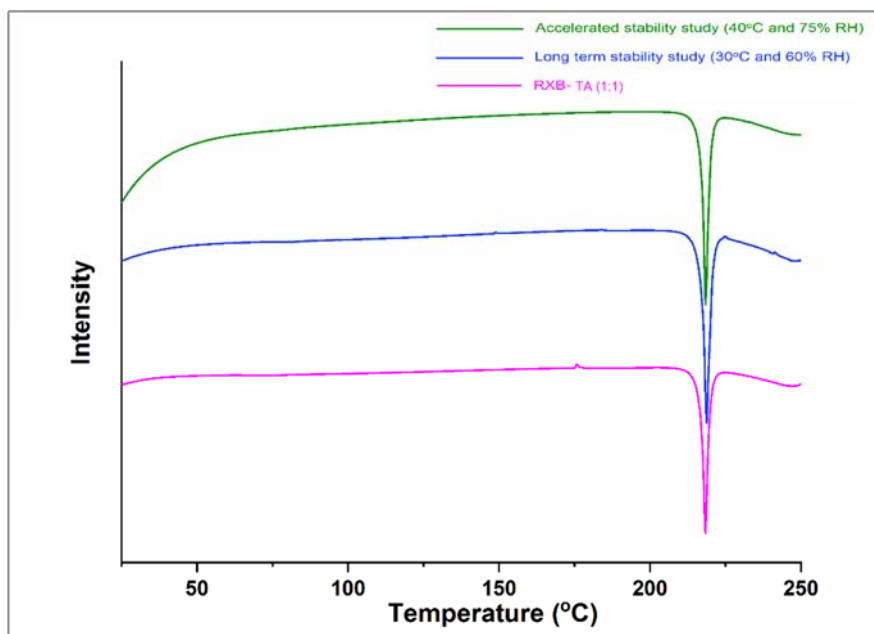


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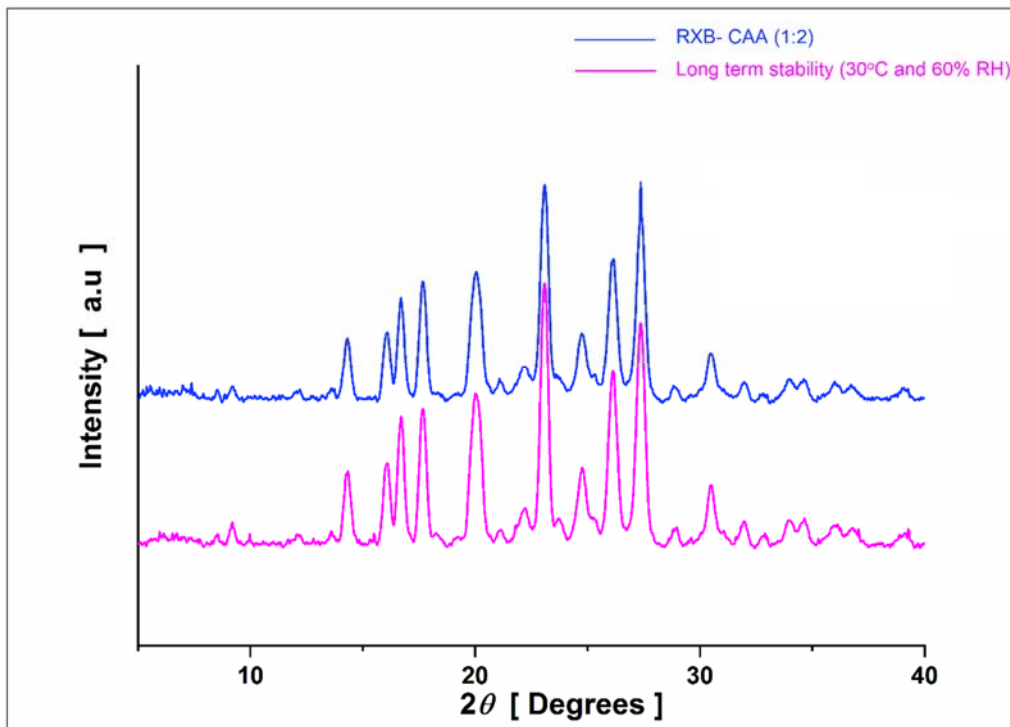


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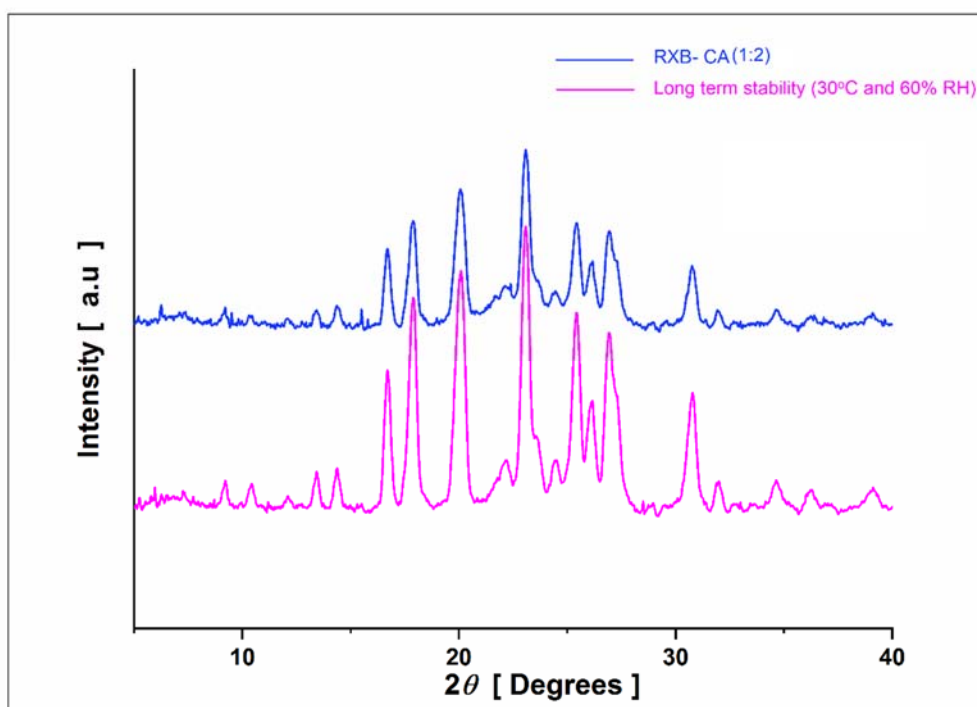


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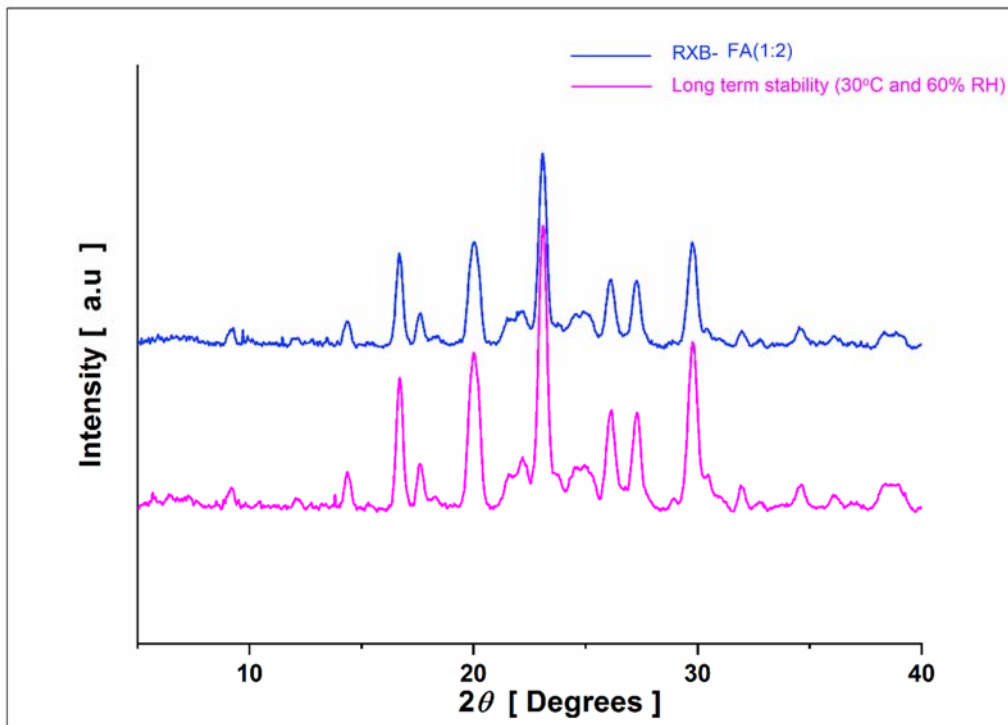
**Figure S5.** DSC profiles of eutectics recorded after accelerated and long-term stability study conditions, (a) RXB- CAA (1:2), (b) RXB- CA (1:2), (c) RXB- FA (1:2), (d) RXB-SA (1:2), (e) RXB- MA (1:4) and (f) RXB- TA (1:1).



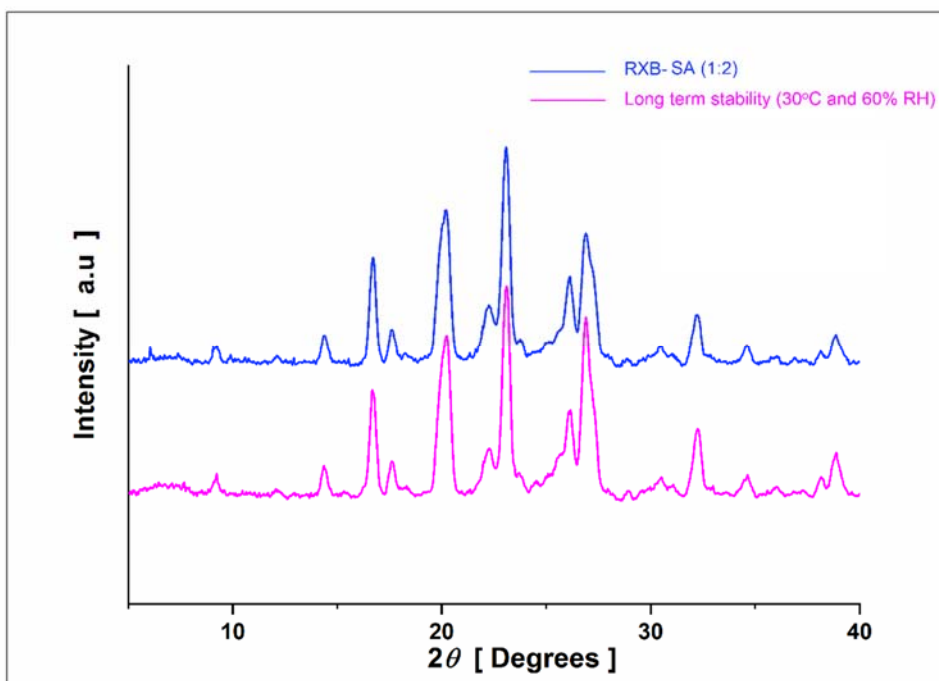
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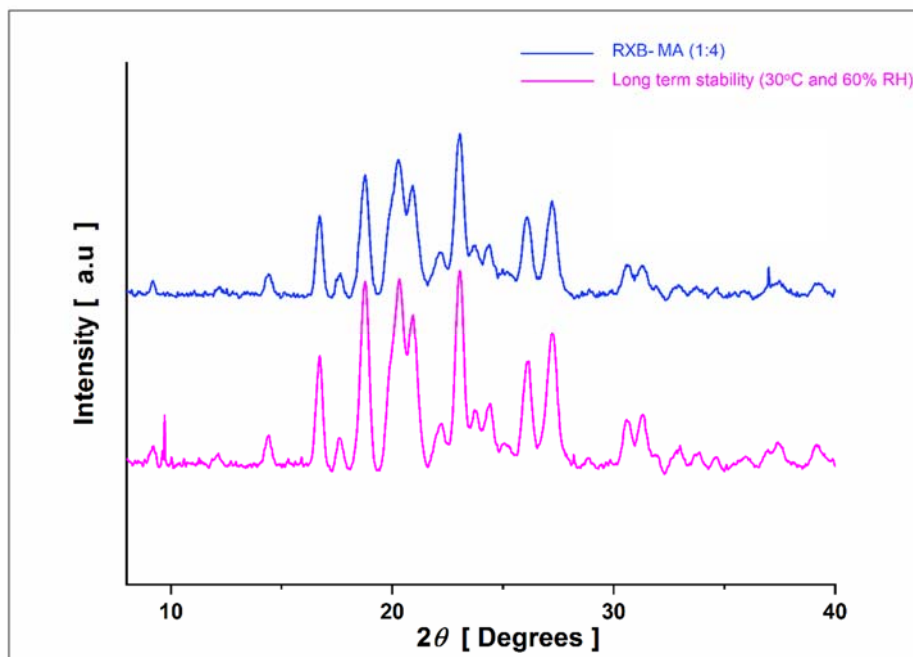
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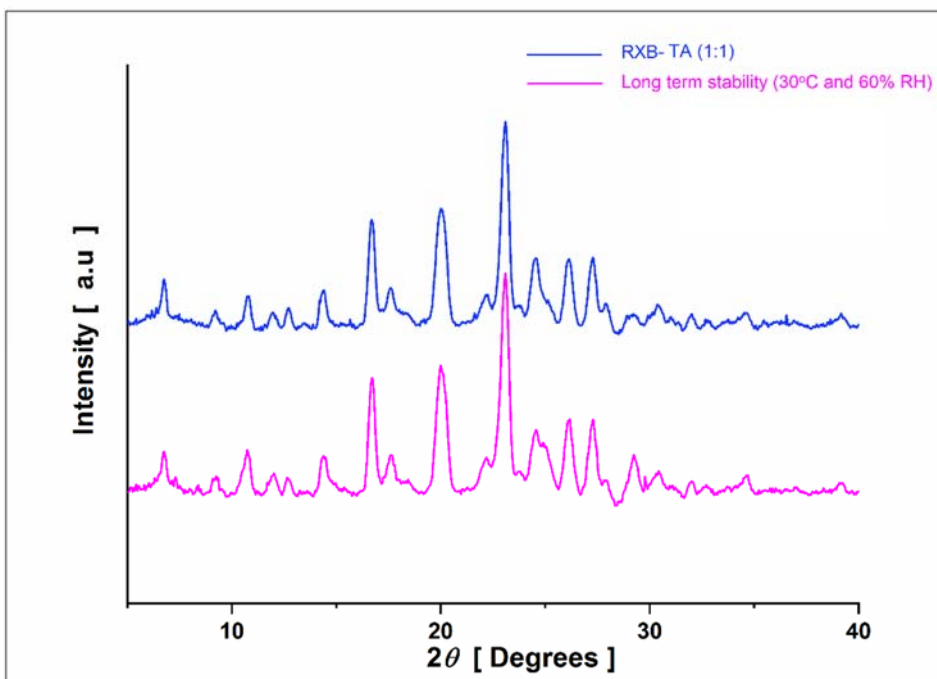
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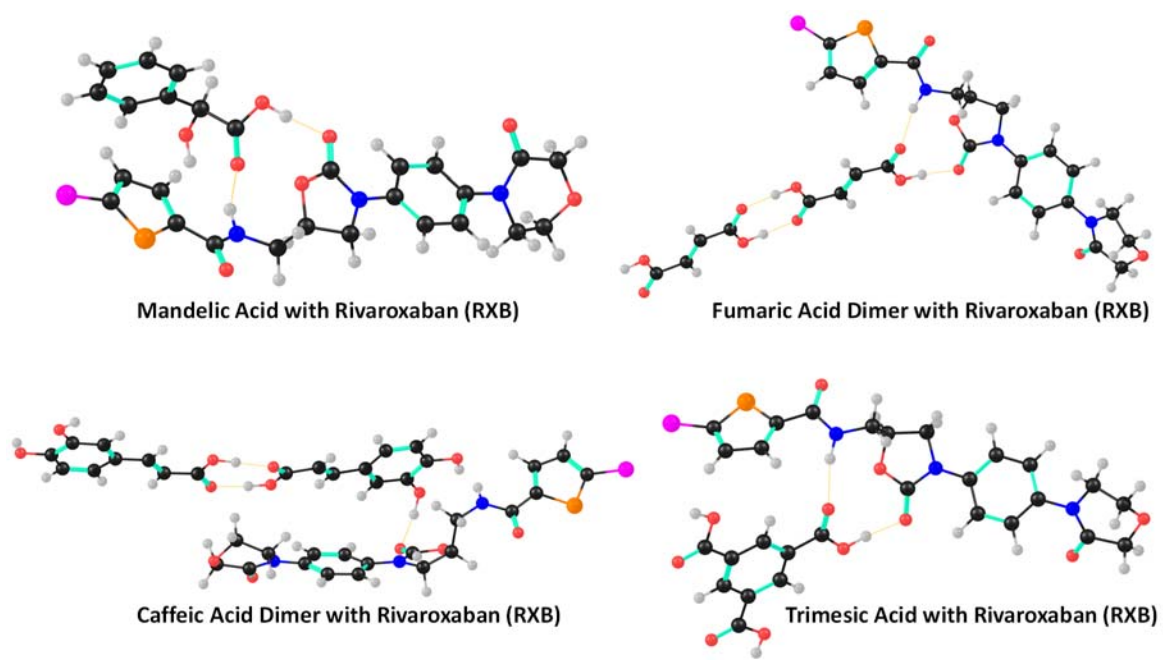


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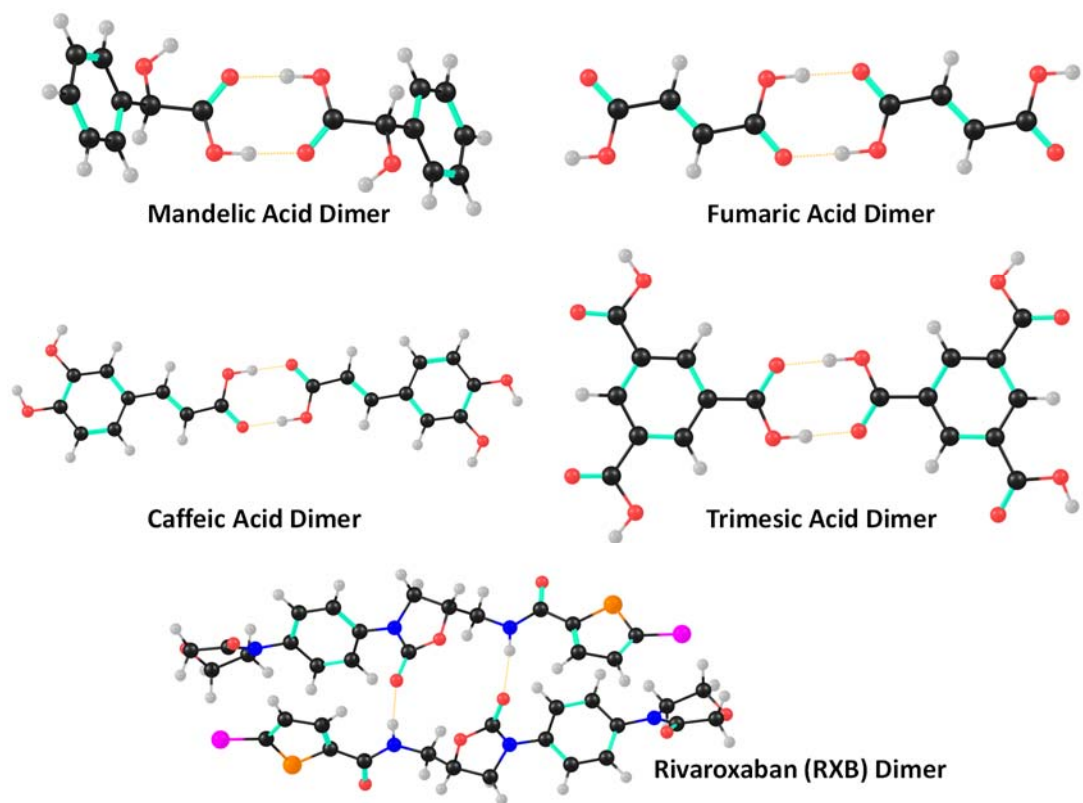


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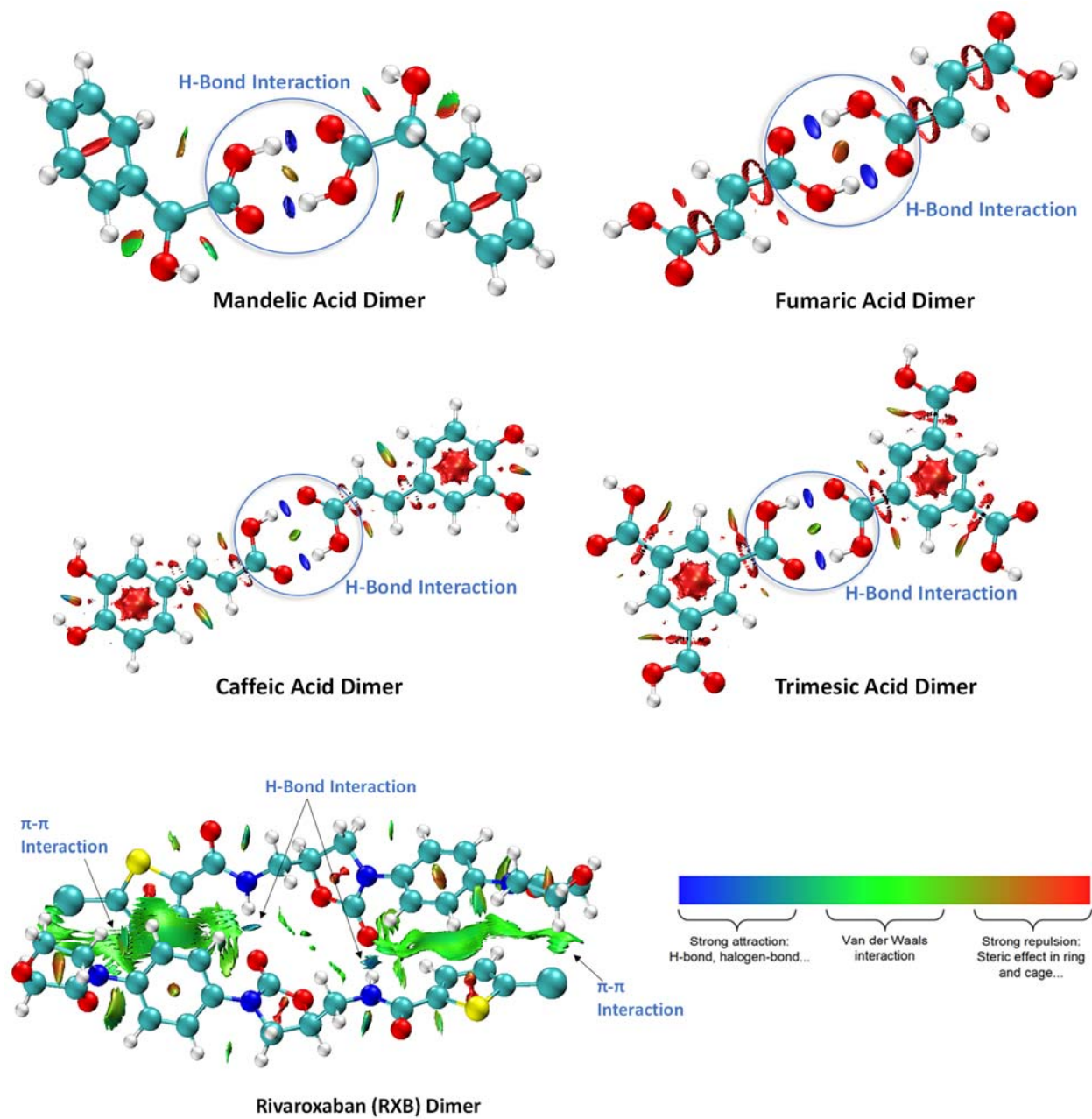
**Figure S6.** PXR D measured for eutectics after long term stability studies, (a) RXB- CAA (1:2), (b) RXB- CA (1:2), (c) RXB- FA (1:2), (d) RXB- SA (1:2), (e) RXB- MA (1:4) and (f) RXB- TA (1:1) suggesting no new crystal phase was formed.



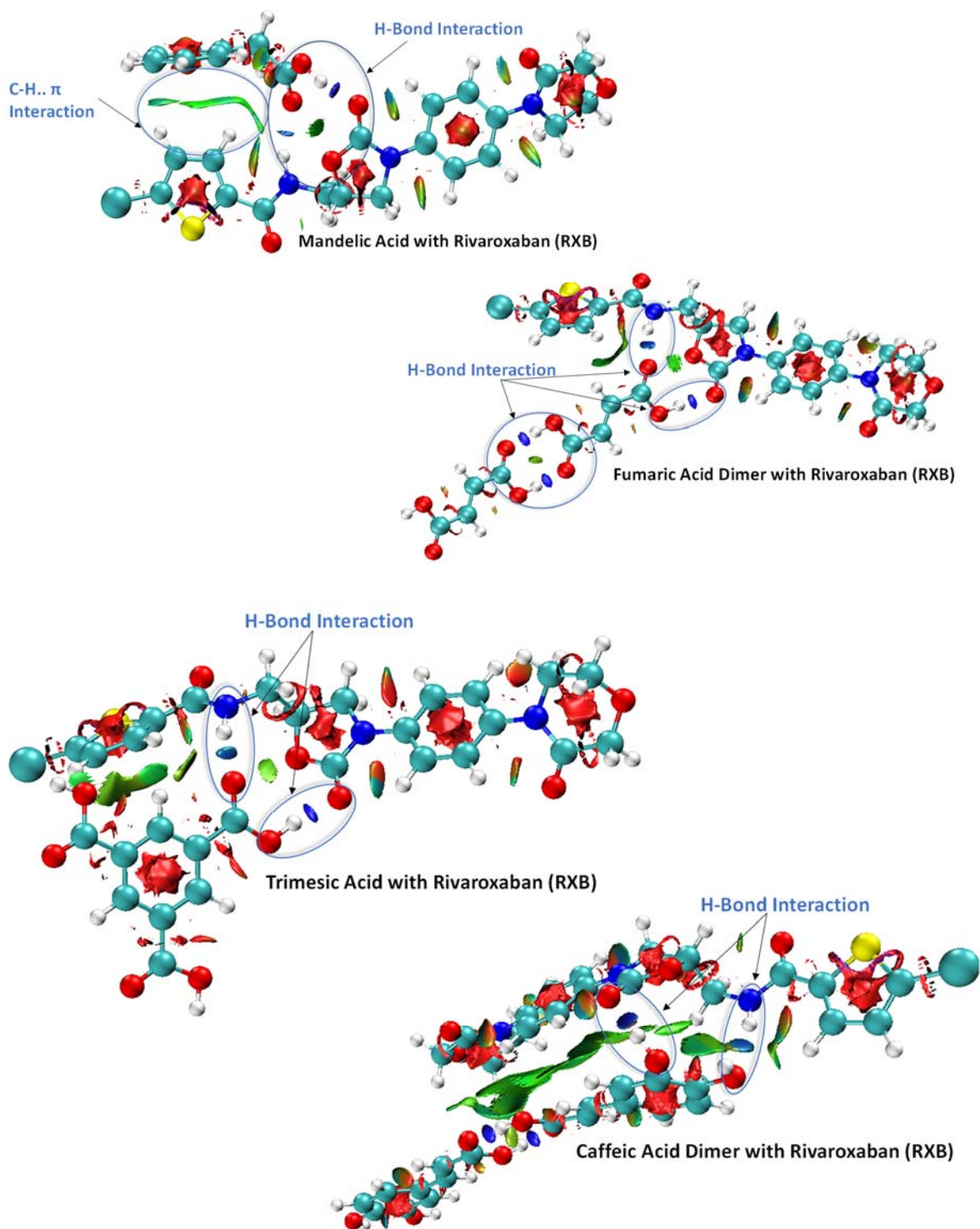
**Figure S7.** The optimized structures of different eutectic system (heterosynthons) at B3LYP/TZVP level of theory.



**Figure S8.** The optimised structures of acids and RXB dimers (homosynthons) at B3LYP/TZVP level of theory.

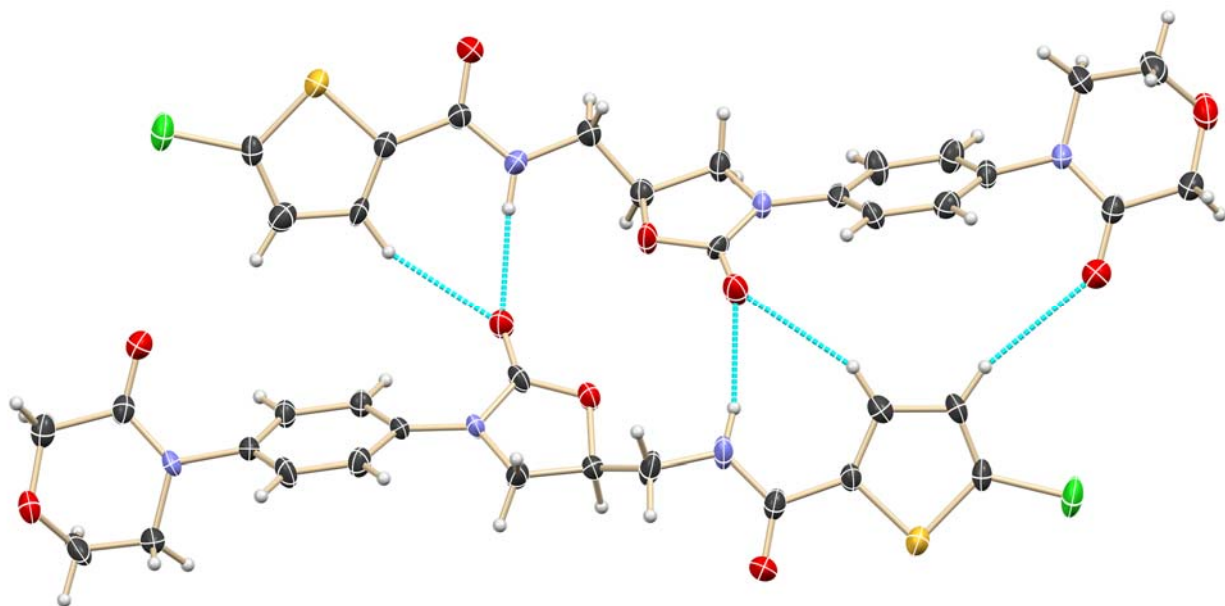


**Figure S9.** The NCI plot for different acids and RXB dimer.



**Figure S10.** The NCI plot for different eutectic systems.





**Figure S11.** The crystal structure of RXB showing dimeric associations similar to predicted structure obtained using DFT studies.

**Table S1.** Samples showing reduction in melting temperature after physical examination.

Sr. No.	Sample (RXB + Coformer)	Reduced melting temperature (x/✓)
1	RXB + Adipic Acid	x
2	RXB + Ascorbic Acid	x
3	RXB + Benzoic Acid	x
4	RXB + Caffeic Acid (RXB-CAA)	✓
5	RXB + Cinnamic Acid	x
6	RXB + Citric Acid	x
7	RXB + Coumaric Acid (RXB-CA)	✓
8	RXB + Fumaric Acid (RXB-FA)	✓
9	RXB + Glutamic Acid	x
10	RXB + Malic Acid	x
11	RXB + Mandelic Acid (RXB-MA)	✓
12	RXB + Oxalic Acid	x
13	RXB + Salicylic acid	x
14	RXB + Stearic Acid	x
15	RXB + Succinic Acid (RXB-SA)	✓
16	RXB + Trimesic Acid (RXB-TA)	✓
17	RXB + Vanillic Acid	x

**Table S2.** Observed vibrational frequencies for eutectics, RXB, CA, RXB-CA (1:2), FA, RXB-FA (1:2), SA, RXB-SA (1:2), MA, RXB-MA (1:4), TA and RXB-TA (1:1).

RXB (cm-1)	CA (cm-1)	RXB-CA (1:2) (cm-1)	FA (cm-1)	RXB-FA (1:2) (cm-1)	SA (cm-1)	RXB-SA (1:2) (cm-1)	MA (cm-1)	RXB-MA (1:4) (cm-1)	TA (cm-1)	RXB-TA (1:1) (cm-1)
3366	3400	3364	1272	3366.5	1302	3368	1431	367	1465	3361
1737	1694	1725	1626	1738	1093	1737.5	1717	1717	1715	1735
832	1449	831	702	830	603	838	-OH peak was merged	835		835
		1433		1623		1311		1432		1468
		1705		1280		1102		1717.5		1713
		-OH peak was merged into -C=O peak		703		604				

**Table S3.** Saturation solubility study of eutectics, RXB, RXB-CAA (1:2), RXB-CA (1:2), RXB-FAA (1:2), RXB-SA (1:2), RXB-MA (1:4) and RXB-TA (1:1) and physical mixtures in distilled water.

Sr. No.	RXB and mixtures (mol:mol)	Saturation solubility for eutectics ( $\mu\text{g/mL}$ ) $\pm$ S.D.	Saturation solubility for physical mixtures ( $\mu\text{g/mL}$ ) $\pm$ S.D.
1	Rivaroxaban (RXB)	$5.49 \pm 0.13$	$5.49 \pm 0.13$
2	RXB-CAA (1:2)	$7.32 \pm 0.22$	$5.51 \pm 0.26$
3	RXB-CA (1:2)	$6.91 \pm 0.19$	$5.47 \pm 0.17$
4	RXB-FA (1:2)	$6.31 \pm 0.22$	$5.45 \pm 0.1$
5	RXB-SA (1:2)	$5.54 \pm 0.33$	$5.44 \pm 0.18$
6	RXB-MA (1:4)	$5.51 \pm 0.27$	$5.45 \pm 0.21$
7	RXB-TA (1:1)	$5.62 \pm 0.28$	$5.42 \pm 0.16$

**Table S4.** Dissolution rate data of RXB and Physical Mixtures (mol:mol), RXB- CAA, RXB- CA, RXB-FA, RXB-SA, RXB-MA and RXB-TA.

<b>Sample Name</b>	<b>% Cumulative Release (at 60 min)</b>
RXB	16.47%
RXB- CAA (1:2)	17%
RXB- CA (1:2)	16.33%
RXB- FA (1:2)	16.90%
RXB- SA (1:2)	16.52%
RXB- MA (1:4)	16.17%
RXB- TA (1:1)	16.64%

**Table S5.** Dissolution rate data of eutectics, RXB, RXB- CAA, RXB- CA and RXB-FA.

Time	RXB (%CR)	RXB- CAA (%CR)	RXB- CA (%CR)	RXB- FA (%CR)
0	0±0	0±0	0±0	0±0
5	0±0	3.17±0.6	1.30±0.51	4.31±0.67
10	0.73±0.5	6.06±1.36	4.86±1.65	9.35±1.75
15	2.30±0.75	8.92±1.76	7.78±0.41	12.13±0.53
20	4.21±1.3	12.44±2.14	11.06±0.97	15.38±1.23
30	8.16±1.78	15.85±1.12	16.13±2.193	19.81±2.33
45	12.04±2.11	21.73±2.34	22.66±2.31	24.50±3.33
60	16.47±3.11	26.37±3.02	27.44±4.02	28.36±2.02

**Table S6.** Theoretical Log P values of RXB and cofomers.

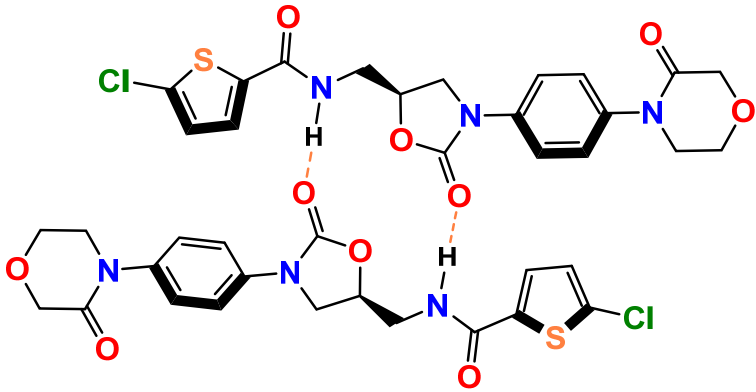
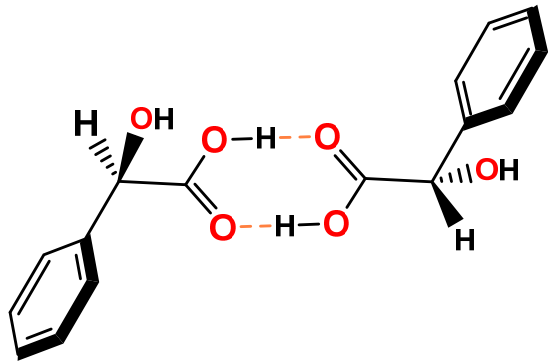
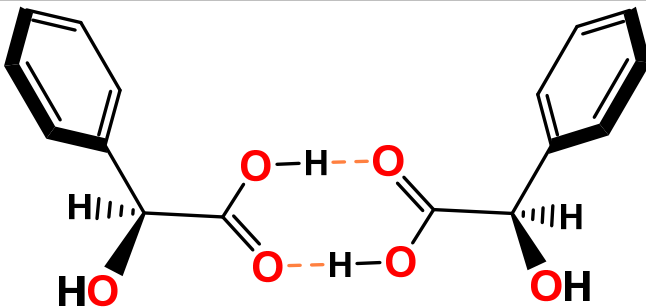
Sr. No.	RXB and Eutectics	logP of RXB and cofomer
1	Rivaroxaban (RXB)	1.5 <sup>a</sup>
2	CAA	1.80 <sup>b</sup>
3	CA	1.71 <sup>b</sup>
4	FA	-0.288 <sup>b</sup>
5	SA	-0.064 <sup>b</sup>
6	MA	0.805 <sup>b</sup>
7	TA	0.78 <sup>b</sup>

## References

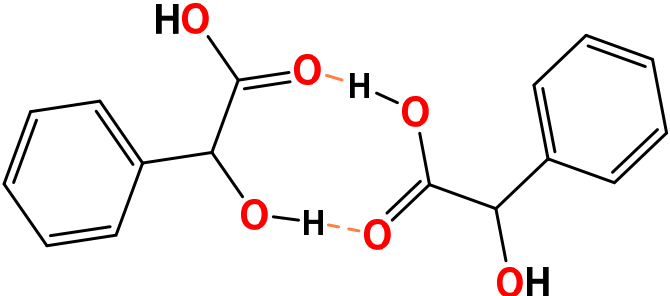
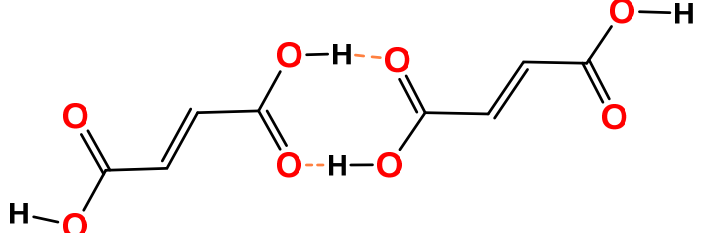
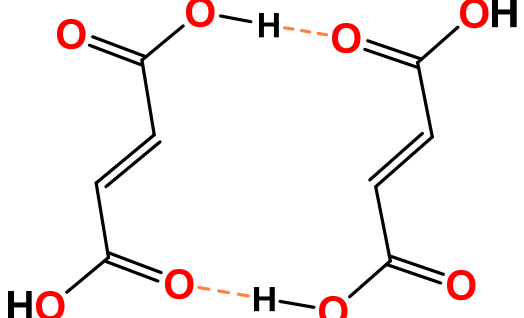
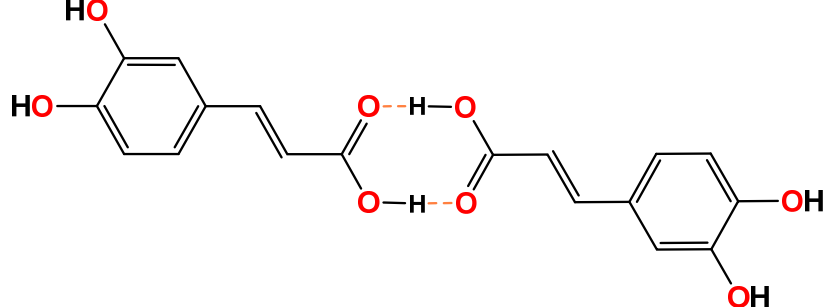
a – W. Mueck, J. Stampfuss, D. Kubitzka and M. Becka M. Clinical pharmacokinetic and pharmacodynamic profile of rivaroxaban. *Clin. Pharmacokinet.* 2014, **53**, 1-16. doi: 10.1007/s40262-013-0100-7

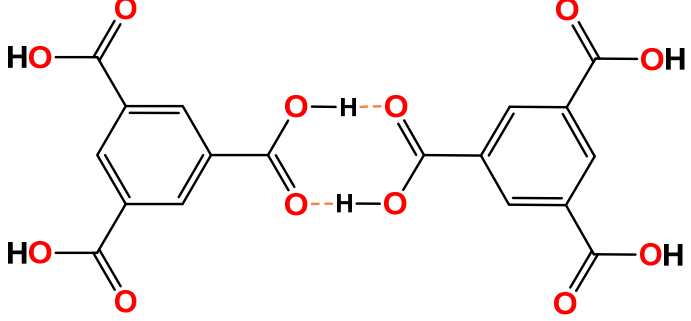
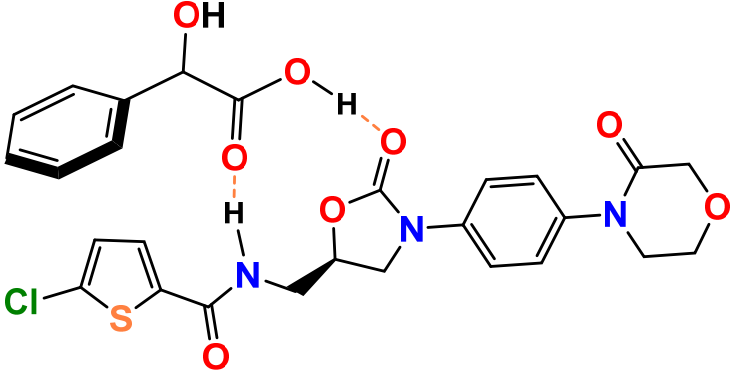
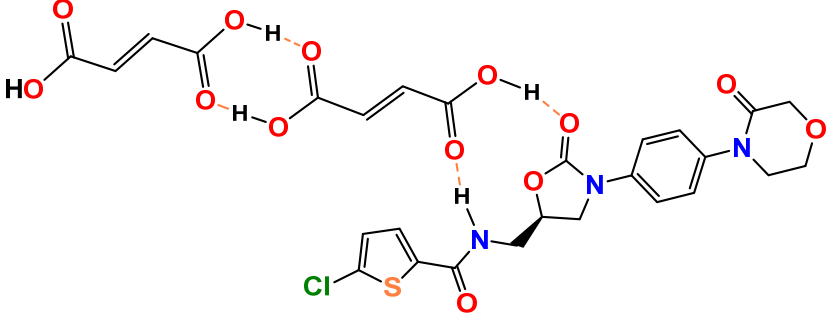
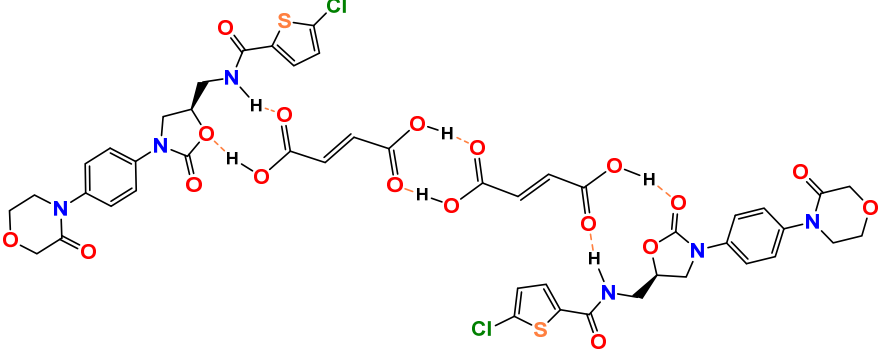
b – Theoretical log P values using Crippen method

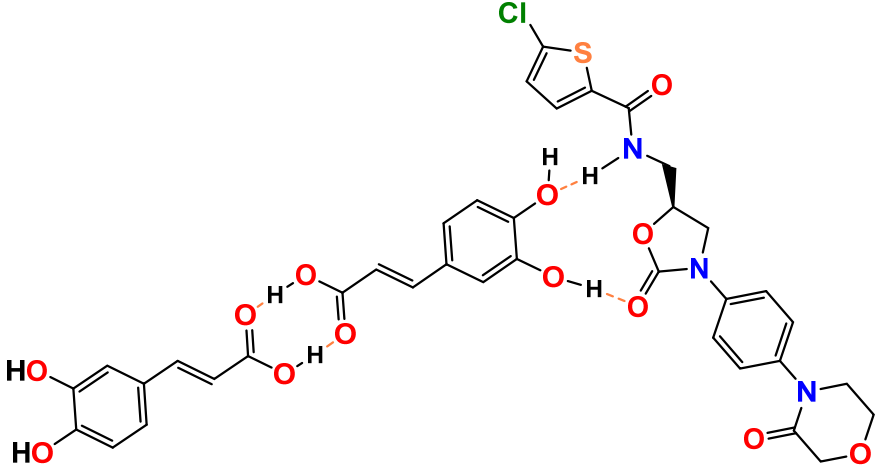
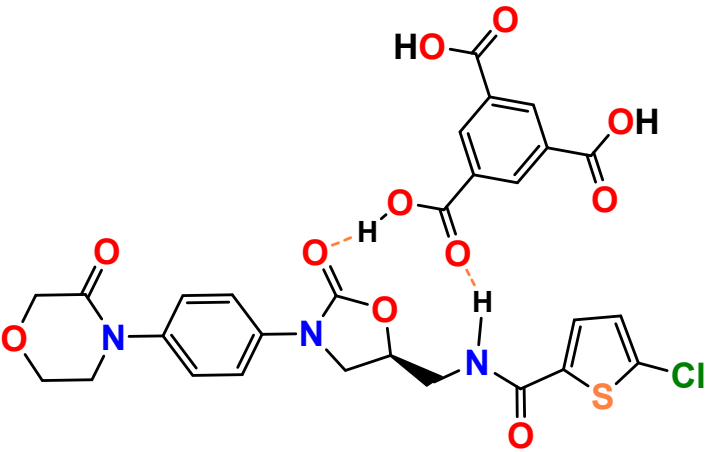
**Table S7.** The interaction energies ( $\Delta E_{\text{int}}$  and  $\Delta G_{\text{int}}$ ) calculated using B3LYP-D3/def-TZVP level of theory.

S.N.	Molecular structure	Interaction Energy (kcal/mol)	
		$\Delta E_{\text{int}}$	$\Delta G_{\text{int}}$
1.	 <p style="text-align: center;">RXB</p>	-29.0	-8.8
2.	 <p style="text-align: center;">Mandelic Acid (MA)</p>	-18.7	-5.8
3.	 <p style="text-align: center;">Mandelic Acid (MA)</p>	-17.6	-4.9



4.	 <p>Mandelic Acid (MA)</p>	-15.1	-2.4
5.	 <p>Fumaric Acid (FA)</p>	-18.9	-6.4
6.	 <p>Fumaric Acid (FA)</p>	-4.2	8.2
7.	 <p>Caffeic Acid (CAA)</p>	-19.8	-6.9

8.	 <p style="text-align: center;">Trimesic Acid (TA)</p>	-19.4	-6.6
9.	 <p style="text-align: center;">RXB-MA (1:1)</p>	-21.5	-5.6
10.	 <p style="text-align: center;">RXB-FA (1:2)</p>	-19.7	-3.3
11.	 <p style="text-align: center;">RXB-FA (1:1)</p>	-9.4	3.2

12.	 <p style="text-align: center;">RXB-CAA (1:2)</p>	-26.9	-5.5
13.	 <p style="text-align: center;">RXB-TA (1:1)</p>	-21.1	-4.5