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Synthesis and Structural Characterization of Novel Salts of Ticlopidine with Enhanced Solubility and Dissolution Rate

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[†] These authors contributed equally.

Content:

- ¹H-NMR Spectra
- Hirshfeld and Fingerprint plots
- Solubility Data
- Dissolution Rate Data

- **¹H-NMR Spectra:**

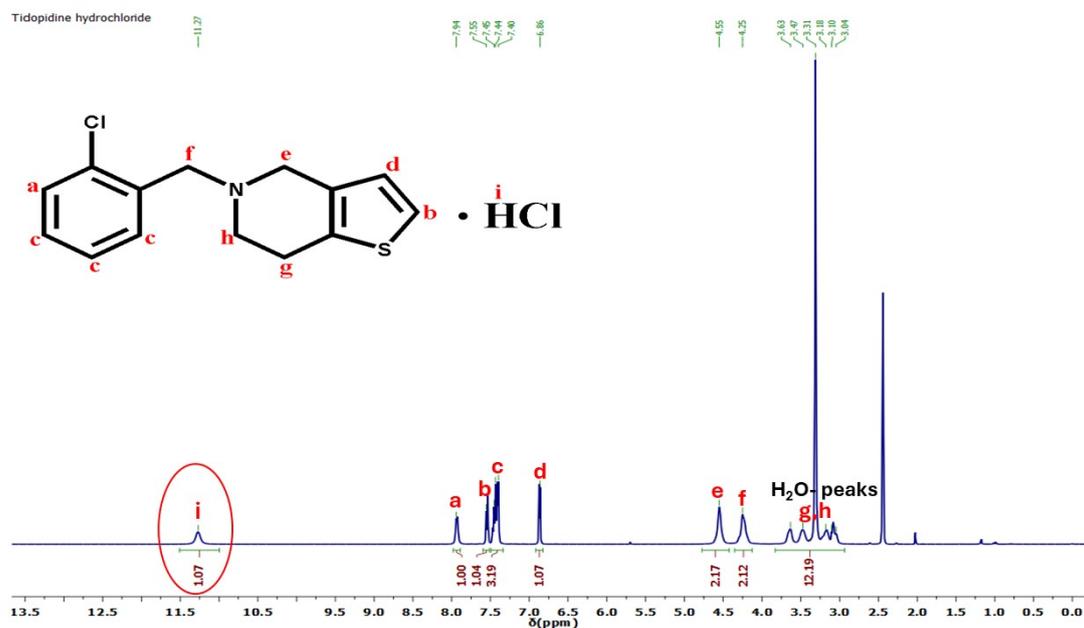
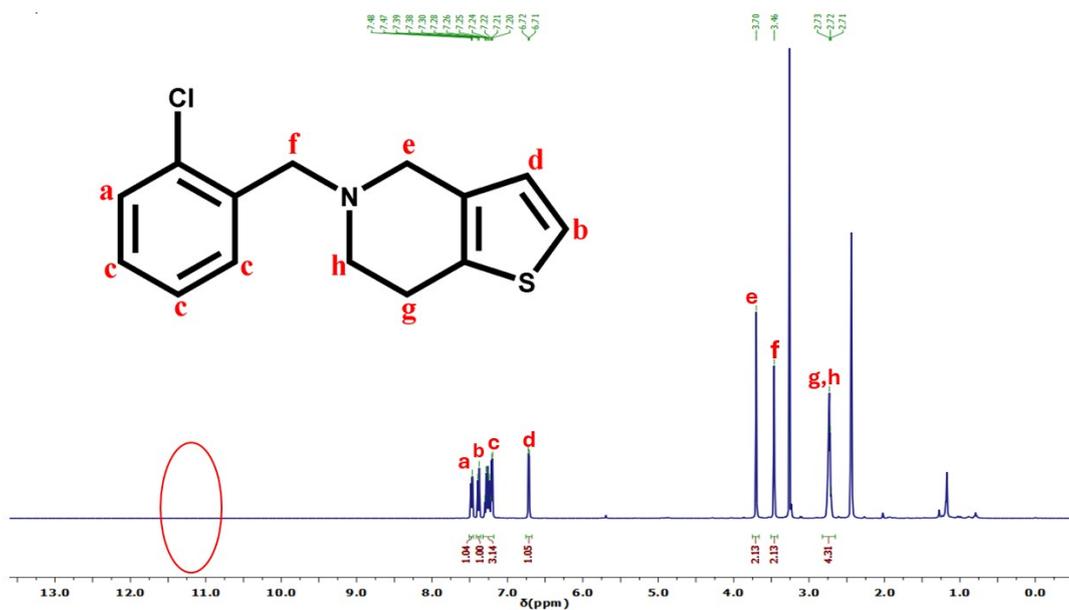


Fig: S1-(a) ¹H-NMR of Ticlopidine hydrochloride



(b) ¹H-NMR of Pure Ticlopidine

- Hirshfeld and Fingerprint plots of Ticlopidine (TPD) Salts:

❖ **TPD: Maleic acid salt**

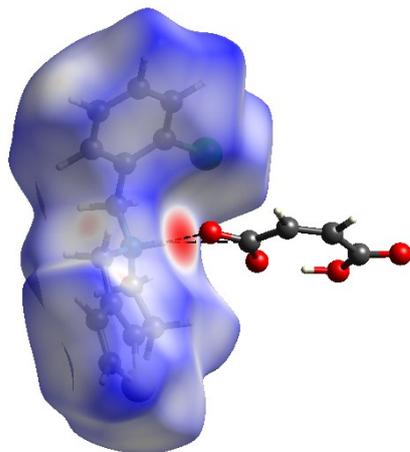
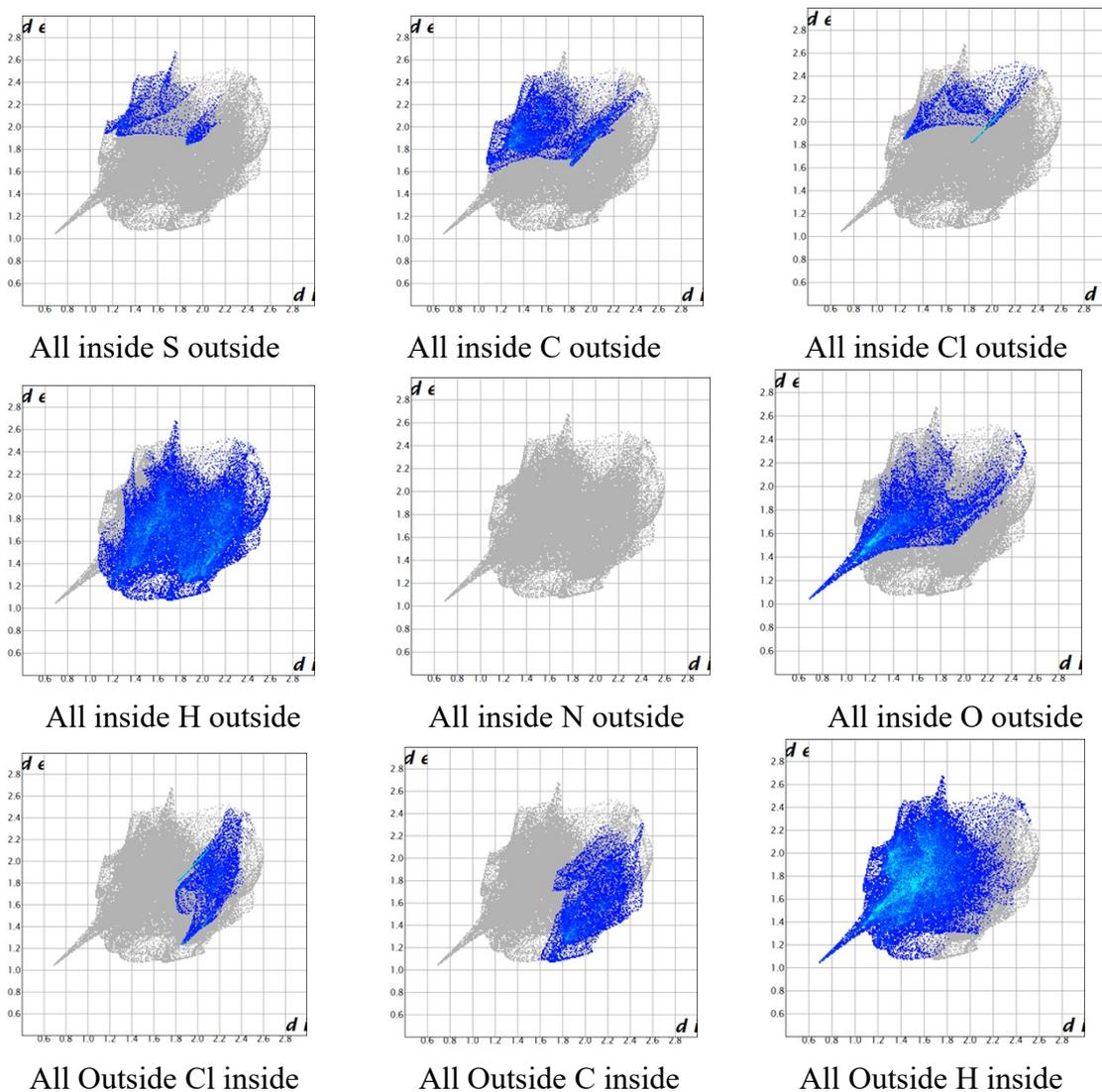
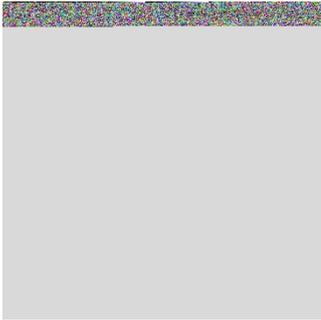
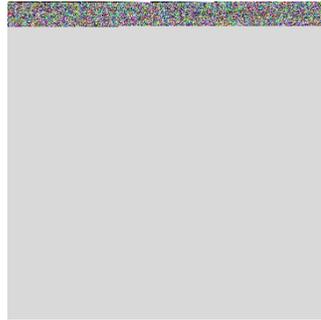


Fig: S2-(a) Hirshfeld surface structure of TPD: Maleic acid salt

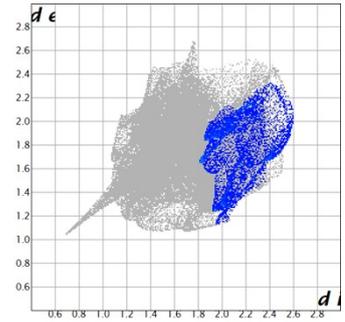




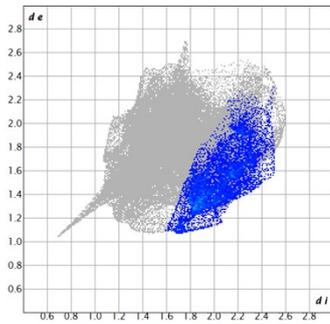
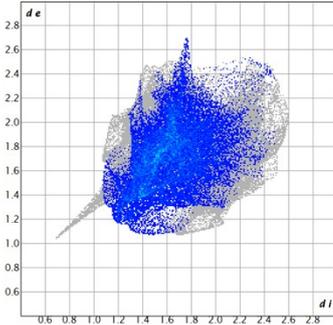
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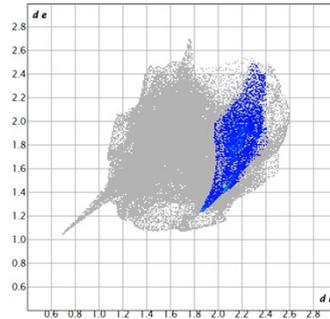
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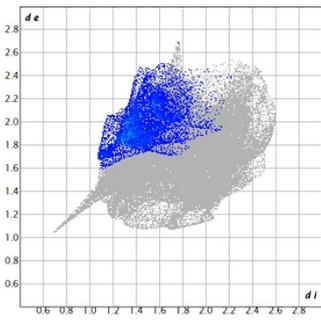
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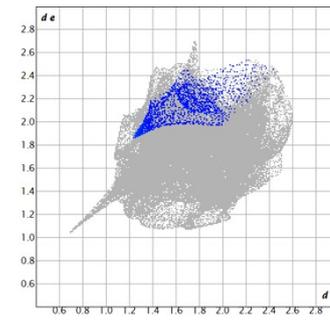
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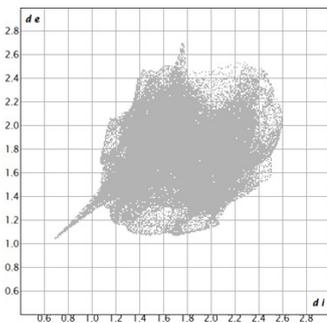
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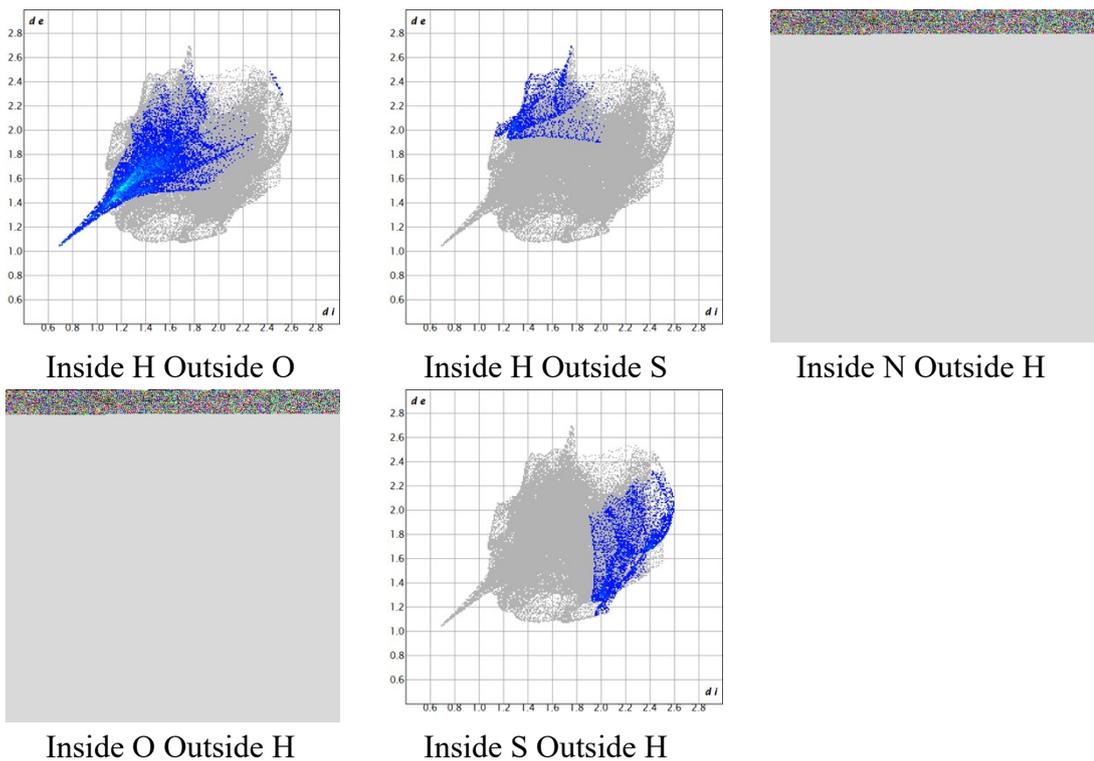


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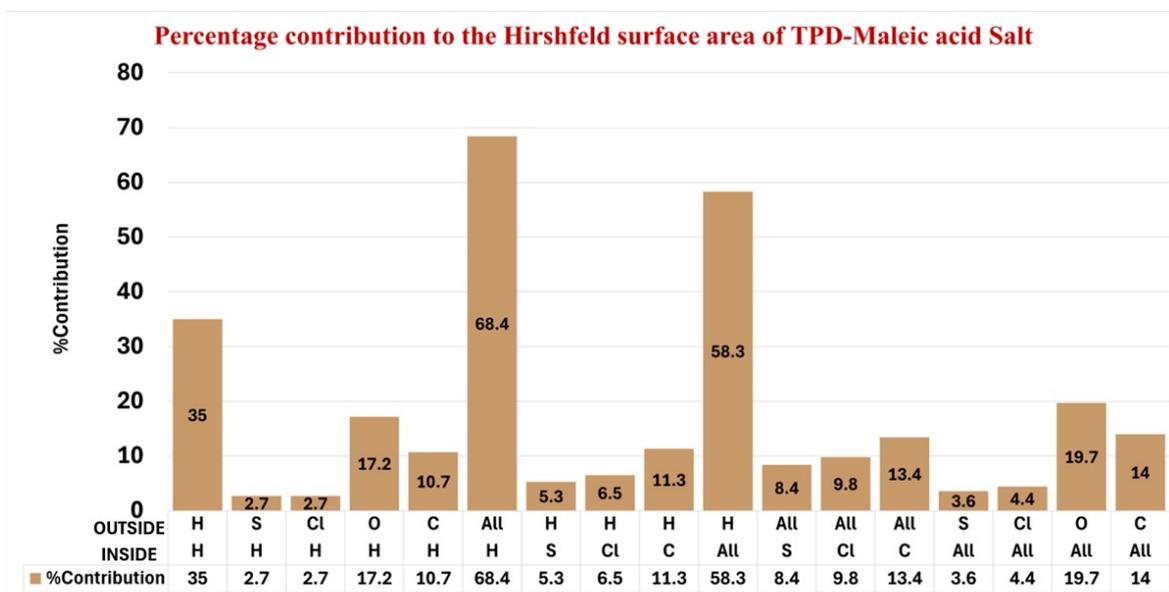


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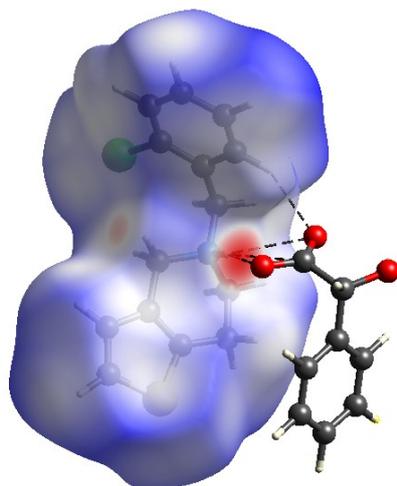
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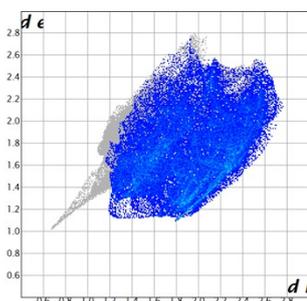
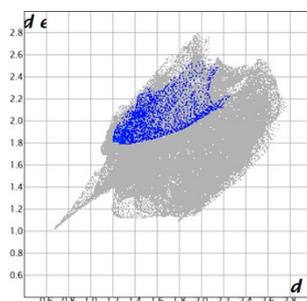
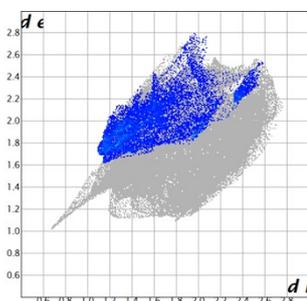
(b) Fingerprint plots of TPD: Maleic acid salt



❖ TPD: Mandelic acid salt



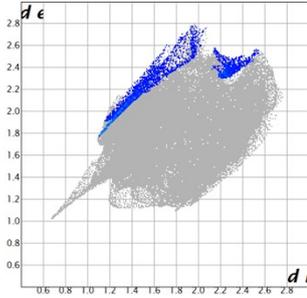
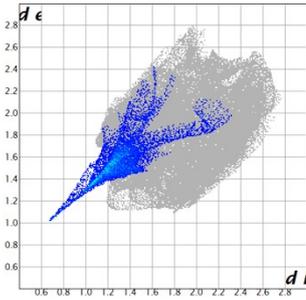
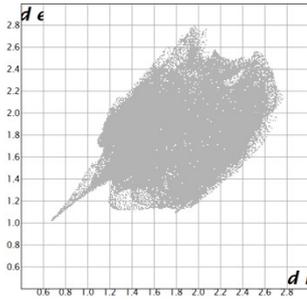
(c) Hirshfeld surface structure of TPD: Mandelic acid salt



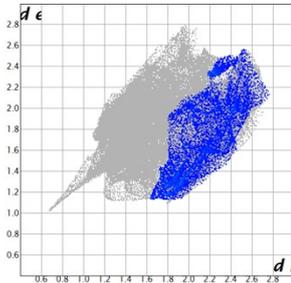
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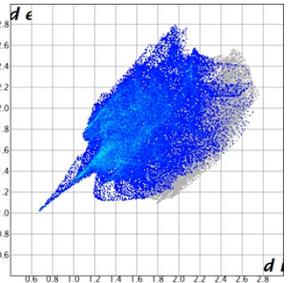
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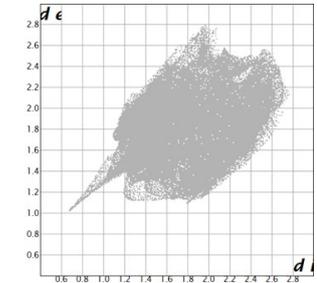
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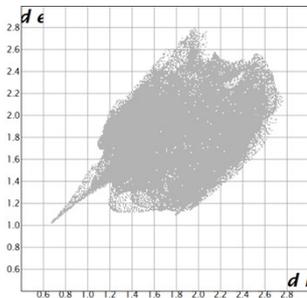
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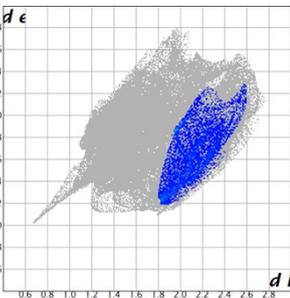
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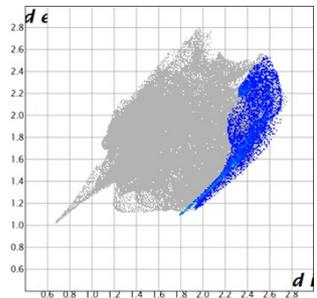
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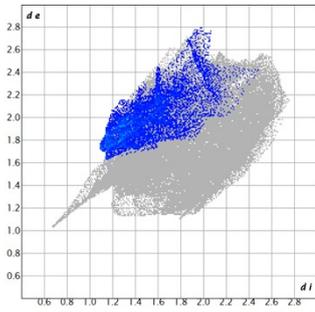
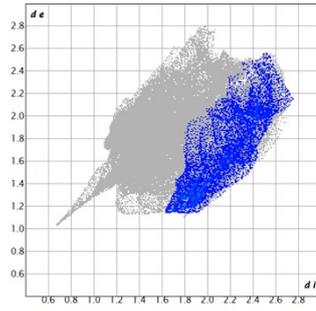
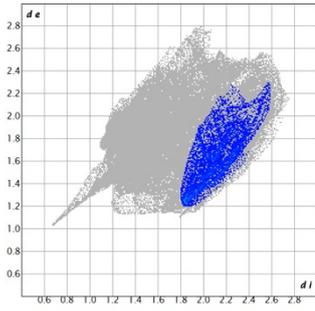
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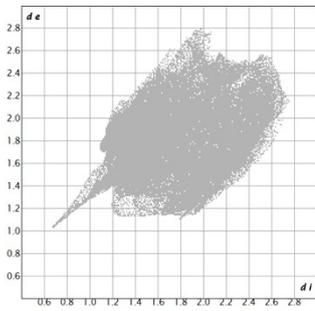
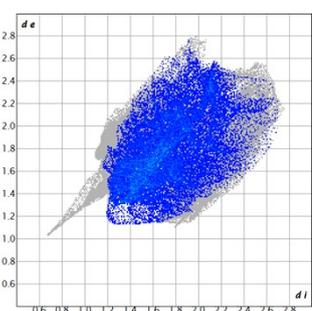
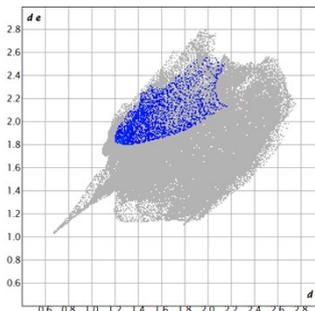
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Inside C1 Outside H

Inside C Outside H

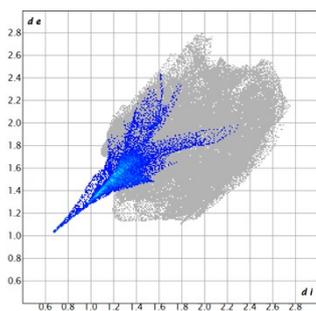
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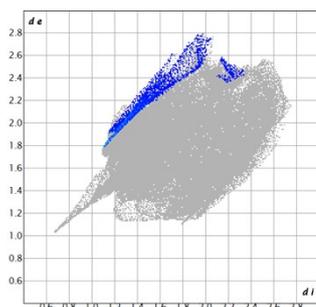
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Inside H Outside H

Inside H Outside N



Inside H Outside O

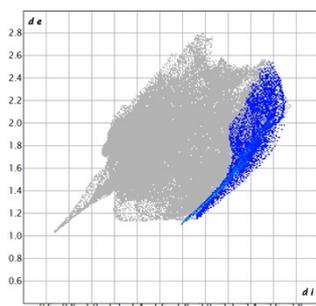


Inside H Outside S

Inside N Outside H

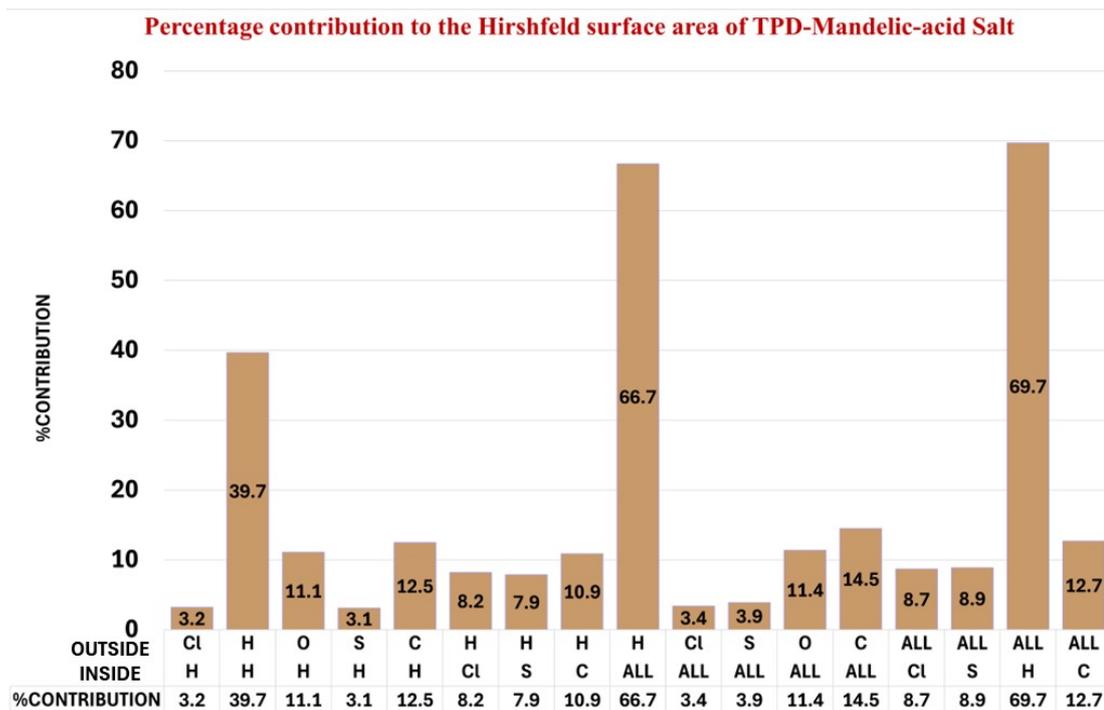


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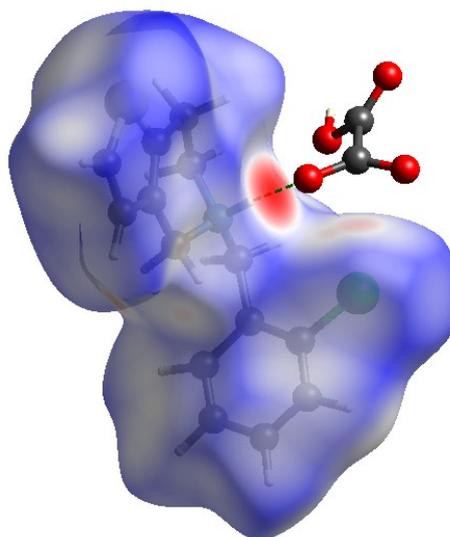


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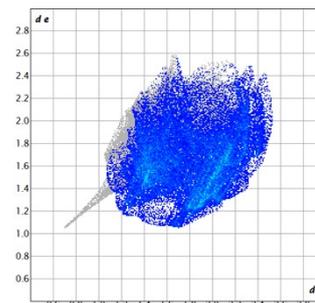
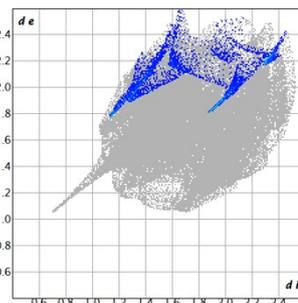
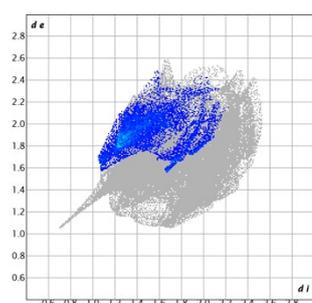
(d) Fingerprint plots of TPD: Mandelic acid salt



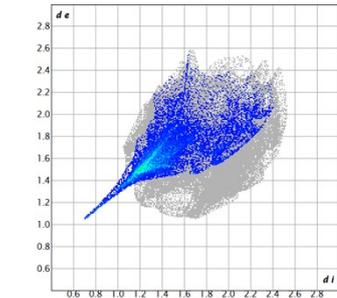
❖ **TPD: Oxalic acid salt**



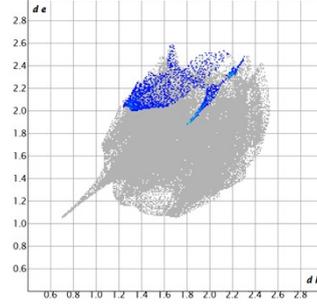
(e) Hirshfeld surface structure of TPD: Oxalic acid salt



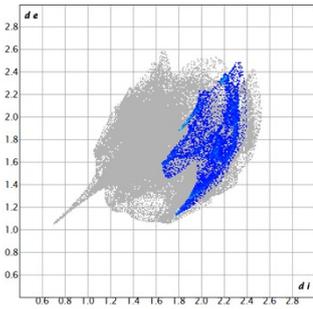
Inside All Outside C



Inside All Outside Cl



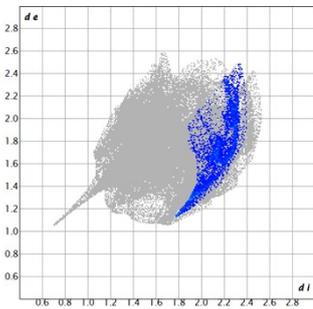
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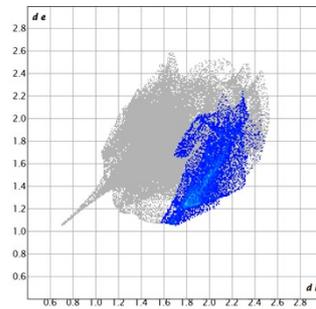
Inside All Outside O

Inside All Outside S

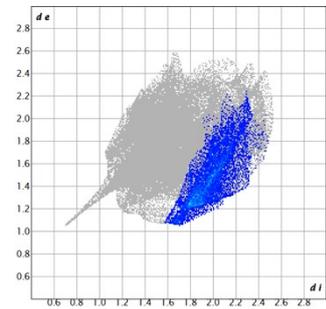
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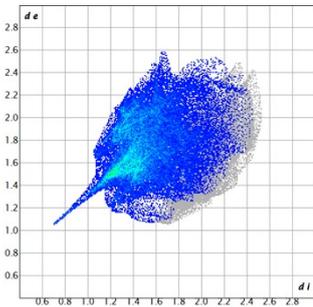
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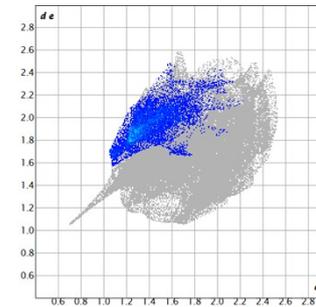
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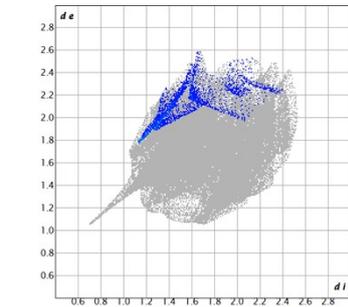
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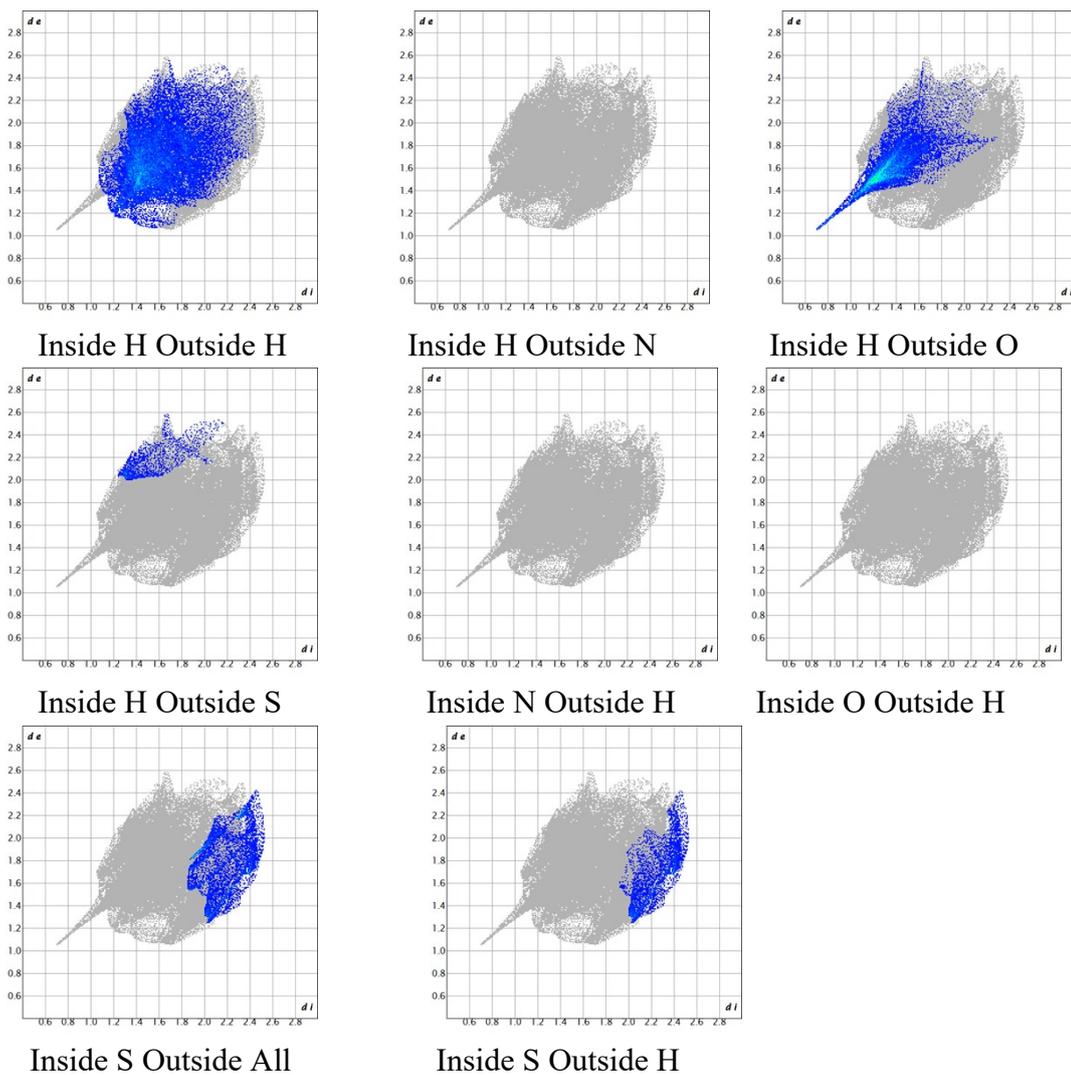
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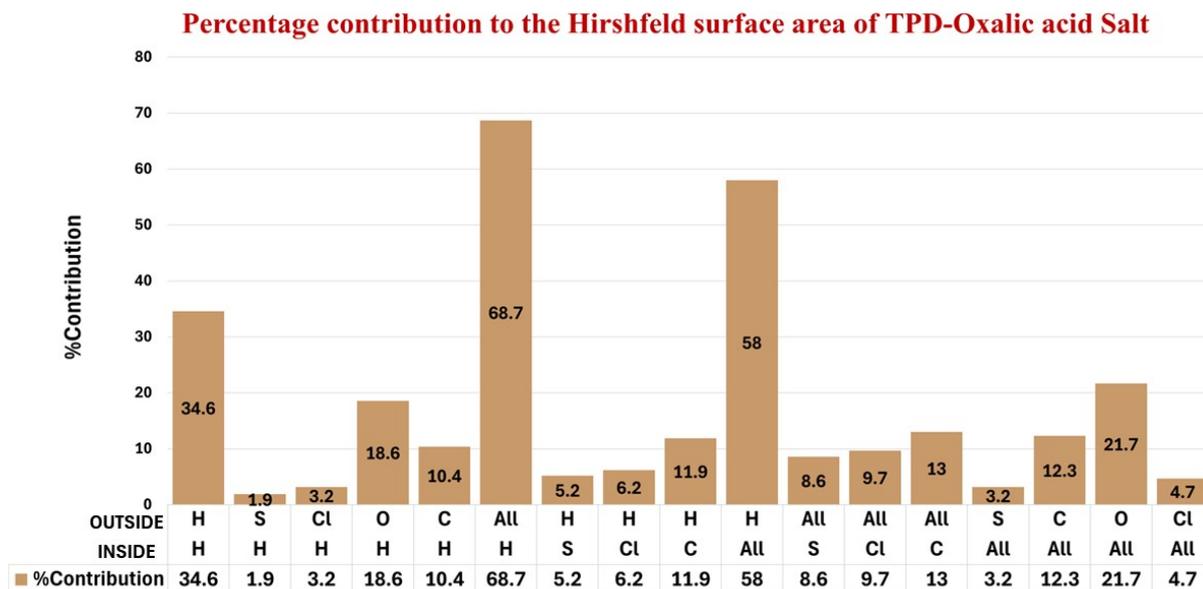
Inside H Outside C



Inside H Outside Cl



(f) Fingerprint plots of TPD: Oxalic acid salt



■ Solubility data of Ticlopidine (TPD) Salts:

One standard calibration curve was prepared (Table S3-a) and then used for determining the solubility of all other compounds. For every salt of Ticlopidine mentioned, a saturated solution was prepared and its concentration was estimated based on the developed calibration curve. This was done because the selected organic acids lacked absorbance maxima in the spectral region equivalent to the λ_{\max} determined for ticlopidine.

Table: S3-(a) Standard Calibration Curve UV-Vis Spectrum Values

Sample Code	Amount of Solvent DDW (ml)	Amount of Oxalic Salt of Ticlopidine (ml)	Concentration (mg/ml)	Absorbance
S1	9	1	0.05	0.0843
S2	8	2	0.1	0.1755
S3	7	3	0.15	0.2217
S4	6	4	0.2	0.3345
S5	5	5	0.25	0.4254
S6	4	6	0.3	0.4585
S7	3	7	0.35	0.5520
S8	2	8	0.4	0.6098
S9	1	9	0.45	0.6820
S10	0	10	0.5	0.7666

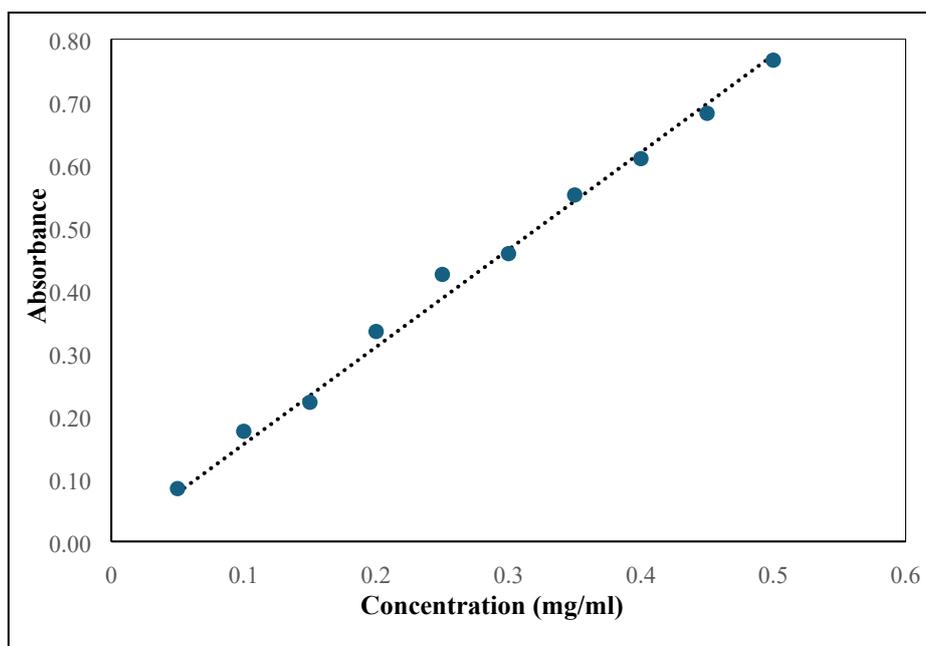


Fig: S3-(a) Standard Calibration curve of TPD: Oxalic acid salt in DDW at 268 nm wavelength.

❖ **TPD: Maleic acid salt**

Sample Code	Amount of DDW (ml)	Amount of Maleic Acid Salt of Ticlopidine (ml)	Concentration (mg/ml)	Absorbance
S1	9	1	0.05	0.0843
S2	8	2	0.1	0.1755
S3	7	3	0.15	0.2217
S4	6	4	0.2	0.3345
S5	5	5	0.25	0.4254
S6	4	6	0.3	0.4585
S7	3	7	0.35	0.5520
S8	2	8	0.4	0.6098
S9	1	9	0.45	0.6820
S10	0	10	0.5	0.7666
Saturated (Dilution Factor = 10)			0.223	0.3457

(b) TPD: Maleic acid salt data, here the solubility is **2.23 mg/ml** at 268 nm in **DDW**

Sample Code	Amount of pH buffer (ml)	Amount of Maleic Acid Salt of Ticlopidine (ml)	Concentration (mg/ml)	Absorbance
S1	9	1	0.05	0.0843
S2	8	2	0.1	0.1755
S3	7	3	0.15	0.2217
S4	6	4	0.2	0.3345
S5	5	5	0.25	0.4254
S6	4	6	0.3	0.4585
S7	3	7	0.35	0.5520
S8	2	8	0.4	0.6098
S9	1	9	0.45	0.6820
S10	0	10	0.5	0.7666
Saturated (Dilution Factor = 10)			0.238	0.3697

(c) TPD: Maleic acid salt data, here the solubility is **2.38 mg/ml** at 268 nm in **pH 2.5**

❖ **TPD: Mandelic acid salt**

Sample Code	Amount of DDW (ml)	Amount of Oxalic Acid Salt of Ticlopidine (ml)	Concentration (mg/ml)	Absorbance
S1	9	1	0.05	0.0843
S2	8	2	0.1	0.1755
S3	7	3	0.15	0.2217
S4	6	4	0.2	0.3345
S5	5	5	0.25	0.4254
S6	4	6	0.3	0.4585
S7	3	7	0.35	0.5520
S8	2	8	0.4	0.6098
S9	1	9	0.45	0.6820
S10	0	10	0.5	0.7666
Saturated (Dilution Factor = 25)			0.338	0.52504

(d) TPD: Mandelic acid salt data, here the solubility is **13.126 mg/ml** at 268 nm in **DDW**

Sample Code	Amount of DDW (ml)	Amount of Oxalic Acid Salt of Ticlopidine (ml)	Concentration (mg/ml)	Absorbance
S1	9	1	0.05	0.0843
S2	8	2	0.1	0.1755
S3	7	3	0.15	0.2217
S4	6	4	0.2	0.3345
S5	5	5	0.25	0.4254
S6	4	6	0.3	0.4585
S7	3	7	0.35	0.5520
S8	2	8	0.4	0.6098
S9	1	9	0.45	0.6820
S10	0	10	0.5	0.7666
Saturated (Dilution Factor = 25)			0.583	0.90451

(e) TPD: Maleic acid salt data, here the solubility is **14.575 mg/ml** at 268 nm in **pH 2.5**

❖ TPD: Oxalic acid salt

Sample Code	Amount of DDW (ml)	Amount of Oxalic Acid Salt of Ticlopidine (ml)	Concentration (mg/ml)	Absorbance
S1	9	1	0.05	0.0843
S2	8	2	0.1	0.1755
S3	7	3	0.15	0.2217
S4	6	4	0.2	0.3345
S5	5	5	0.25	0.4254
S6	4	6	0.3	0.4585
S7	3	7	0.35	0.5520
S8	2	8	0.4	0.6098
S9	1	9	0.45	0.6820
S10	0	10	0.5	0.7666
Saturated (Dilution Factor = 10)			0.269	0.4172

(f) TPD: Mandelic acid salt data, here the solubility is **2.69 mg/ml** at 268 nm in **DDW**

Sample Code	Amount of DDW (ml)	Amount of Oxalic Acid Salt of Ticlopidine (ml)	Concentration (mg/ml)	Absorbance
S1	9	1	0.05	0.0843
S2	8	2	0.1	0.1755
S3	7	3	0.15	0.2217
S4	6	4	0.2	0.3345
S5	5	5	0.25	0.4254
S6	4	6	0.3	0.4585
S7	3	7	0.35	0.5520
S8	2	8	0.4	0.6098
S9	1	9	0.45	0.6820
S10	0	10	0.5	0.7666
Saturated (Dilution Factor = 10)			0.258	0.4002

(g) TPD: Maleic acid salt data, here the solubility is **2.58 mg/ml** at 268 nm in **pH 2.5**

▪ **Dissolution Rate of Ticlopidine (TPD) Salts:**

Time (min)	TPD:Oxalic acid salt(DDW)	TPD:Oxalic acid salt(pH 2.5)	TPD:Maleic acid salt(DDW)	TPD:Maleic acid salt(pH 2.5)
5	0.29	0.29	0.30	0.12
10	0.35	0.45	0.42	0.26
15	0.36	0.51	0.47	0.38
30	0.43	0.57	0.58	0.46
45	0.50	0.65	0.66	0.77
60	0.53	0.68	0.73	0.92
90	0.95	0.77	0.84	1.15
120	1.60	0.92	1.03	1.33