Electronic Supplementary Information†

Highly soluble olanzapinium maleate crystalline salts †

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Crystallization Experimental

Single crystals

Olanzapinium monomaleate 1:1 salt

30 mg (0.1 mmol) of olanzapine and 6 mg (0.05 mmol) of maleic acid were taken in a mortar-pestle, 10-15 drops of ethyl acetate was added, the material was manually ground for 15 min, and then dissolved in 15 mL ethyl acetate-acetone mixture and left for slow evaporation at room temperature.

Olanzapinium dimaleate 1:2 salt

30 mg (0.1 mmol) of olanzapine, 17 mg (0.1 mmol) of aspirin and 6 mg (0.05 mmol) of maleic acid were taken in a mortar-pestle, 10-15 drops of ethyl acetate was added, the material was manually ground for 15 min, and then dissolved in 20 mL ethyl acetate-nitromethane mixture and left for slow evaporation at room temperature.

Powder material

Amorphous salts of olanzapine and maleic acid

To prepare the 1:1 and 1:2 salt, 30 mg (0.1 mmol) of olanzapine was mixed with the stoichiometric amount of maleic acid required in a mortar-pestle and manually ground for 10-15 min without the addition of any solvent (neat grinding). The resultant solid was characterized by XRPD, thermal and spectral methods.

Crystalline salts of olanzapine and maleic acid

1:1 and 1:2 crystalline salts were prepared by mixing 30 mg (0.1 mmol) of olanzapine with the stoichiometric amount of maleic acid required in a mortar-pestle, 10-15 drops of acetonitrile was added and manually ground for 15-20 min (liquid-assisted grinding). The resultant solid was characterized by XRPD, thermal and spectral methods. The XRPD of the bulk material matched with the calculated lines for the crystal structure.

Table S1 Crystallographic data of olanzapinium maleate 1:1 and 1:2 salts.

Compound	Olanzapinium mononmaleate 1:1 salt	Olanzapinium dimaleate 1:2 salt
chemical formula	$C_{21}H_{24}N_4O_4S$	$C_{25}H_{28}N_4O_8S$
formula weight	428.50	544.57
crystal system	monoclinic	Triclinic
space group	$P2_1/n$	$P\bar{1}$
T/K	298(2)	298(2)
a/Å	10.852(5)	8.518(3)
b/Å	13.748(7)	9.804(4)
c/Å	13.879(7)	16.210(6)
α/°	90	95.956(7)
β/°	97.856(8)	97.945(7)
γ/°	90	107.789(7)
Z	4	2
V/Å^3	2051.3(17)	1261.2(8)
D_{calc}/g cm^{-3}	1.387	1.434
μ/mm^{-1}	0.194	0.186
reflns collected	20986	13184
unique reflns	4054	4971
observed reflns	3375	3737
$R_1[I > 2\sigma(I)]$	0.0418	0.0864
wR_2 [all]	0.1125	0.1789
goodness-of-fit	1.068	1.243
diffractometer	SMART-APEX CCD	SMART-APEX CCD

Table S2 Hydrogen bonds in crystal structures of olanzapinium maleate 1:1 and 1:2 salts. O–H, N–H and C–H distances are neutron-normalized to 0.983, 1.009 and 1.083 Å.

Interaction	H···A/ Å	D···A/ Å	∠D–H···A/ º	Symmetry code
Olanzapinium monomaleate 1:1 salt				
$N3^+$–H3···$O4^-$	1.70	2.648(2)	155.5	---

N4–H4···O1	2.04	3.018(3)	161.9	½–x, –½+y, 3/2–z
C16 –H16A···N4	2.53	3.537(3)	155.1	½+x, ½–y, ½+z
C18–H18B···N1	2.25	2.680(3)	101.0	[a]
Olanzapinium dimaleate 1:2 salt				
$N1^{+}$–H1···$O1^{-}$	1.86	2.825(5)	159.2	1–x, –y, 1–z
$N3^{+}$–H3···$O5^{-}$	1.66	2.656(5)	170.1	x, –1+y, z
N4–H4···O1	1.89	2.885(5)	166.6	x, y, –1+z
C10–H10A···O7	2.44	3.397(6)	146.4	1+x, y, z
C15–H15A···O6	2.35	3.348(6)	151.8	x, –1+y, z
C19–H19A···$O5^{-}$	2.29	3.359(6)	170.9	2–x, 1–y, 1–z
C19–H19B···O8	2.32	3.290(7)	148.8	1–x, 1–y, 1–z

[a] Intramolecular hydrogen bond.

Table S3 FT-IR characterization of the olanzapinium maleate salts.

	Olanzapine base	Maleic acid	Crystalline olanzapinium monomaleate (1:1 salt)	Amorphous olanzapinium monomaleate (1:1 salt)	Crystalline olanzapinium dimaleate (1:2 salt)	Amorphous olanzapinium dimaleate (1:2 salt)
N–H Stretching	3442.2 (asym) 3220.6 (sym)	–	3441.4 (asym) 3260.9 (sym)	3430.7 (asym) 3242.5 (sym)	3435.3 (asym) 3253.3 (sym)	3431.4 (asym) 3245.0 (sym)
O–H Stretching	–	3058.6	3057.1	3050.7	3120.1	3115.9
benzene ring C–H stretching	3013.1	–	3018.9	3016.8	3017.7	3013.8
C–H stretching (of CH_3)	2933.3, 2837.3	2921.4	2920.4, 2859.0	2926.2, 2844.1	2958.5	2927.7
C=C stretching (aromatic)	1470.3	–	1468.5	1467.2	1470.7	1508.8
C=O stretching	–	1706.8	1699.0	1701.4	1703.2	1701.4
N–H bending	1585.1	–	1591.3	1589.7	1585.0	1588.8
C=O bending	–	1264.6	1368.6	1352.1	1383.1	1383.9

A strong interaction results in red shift for N–H stretching frequency.

Table S4 FT-NIR characterization of the olanzapinium maleate salts.

	Olanzapine base	Maleic acid	Crystalline olanzapinium monomaleate (1:1 salt)	Amorphous olanzapinium monomaleate (1:1 salt)	Crystalline olanzapinium dimaleate (1:2 salt)	Amorphous olanzapinium dimaleate (1:2 salt)
Ar C–H first overtone	5959.8, 5890.4	–	5932.5, 5874.3	5951.5, 5785.9	5962.3	5953.3
O–H first overtone	–	5980.2				
C=O second overtone	–		5164.4 (new)	5164.4 (new)	5104.2 (new)	5158.6 (new)
N–H combination	4846.9, 4770.9, 4645.0	–				
N–H + O–H combination	–	–	4733.2, 4665.1	4739.5, 4655.6	4736.3, 4661.1	4738.0, 4667.5
O–H + C=O combination	–	4758.5				
C–H combination	4428.8, 4356.2, 4315.8, 4257.8, 4149.3, 4084.5	4492.3, 4426.9, 4384.5, 4320.0, 4273.5	4428.7, 4393.2, 4310.3, 4269.2, 4165.6, 4081.7	4426.1, 4321.8, 4083.8	4441.7, 4406.3, 4331.9, 4181.8	4434.7, 4318.1, 4249.9, 4083.7

Table S5 FT-Raman characterization of the olanzapinium maleate salts.

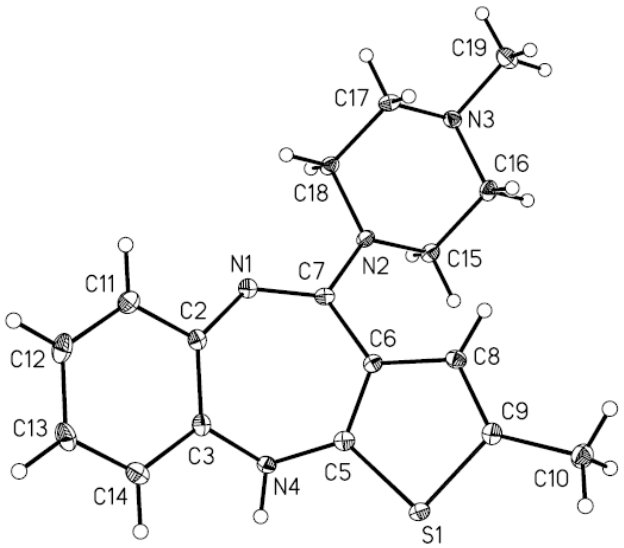
	Olanzapine base	Maleic acid	Crystalline olanzapinium monomaleate (1:1 salt)	Amorphous olanzapinium monomaleate (1:1 salt)	Crystalline olanzapinium dimaleate (1:2 salt)	Amorphous olanzapinium dimaleate (1:2 salt)
N–H Stretching	3061.6	–	3064.7	3055.8	3071.5	3046.9
benzene ring C–H stretching	2988.5	–	2989.9	2997.7	2988.3	3005.8
C–H stretching (of CH_3)	2940.3 2916.1	3059.2	2950.8 2920.5	2953.2 2921.5	2964.2 2935.9	2962.3 2926.5
C=O stretching	–	1700.4	1698.1	1696.5	1698.0	1702.3
N–H bending	1517.9	–	1515.6	1516.4	1591.4	1608.6
C=O bending	–	1330.6	1370.8	1381.8	1379.6	1382.9

Table S6 ss-NMR chemical shift (δ, ppm) and peak assignment for olanzapinium maleate salts.

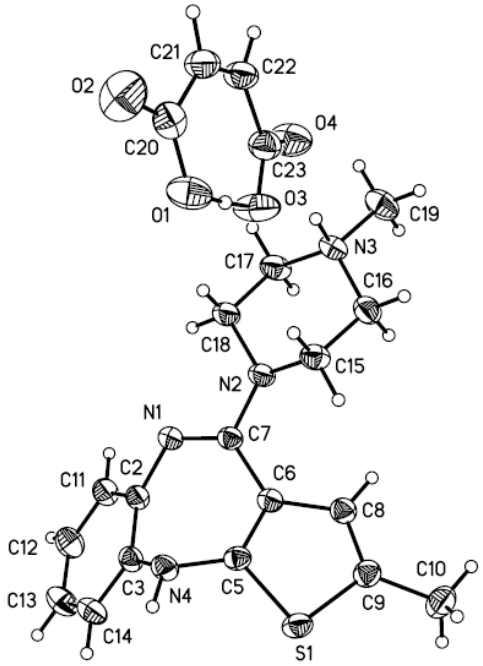
Sites	Olanzapine	Crystalline 1:1 salt	Amorphous 1:1 salt	Crystalline 1:2 salt
^{13}C				
C10	15.59	14.64	15.55	16.70

C18	44.30	43.30	43.93	42.18
C15	45.68	47.30	45.73	43.96
C16	52.85	51.93	52.75	50.79
C17	53.32	52.61	53.32	52.24
C19	48.26	41.53	48.23	47.24
C14	116.49	123.54	120.20	104.35
C13	120.27	125.16	121.12	123.13
C12	120.99	127.06	122.04	124.79
C8	122.00	128.59	122.96	127.09
C11	123.44	133.39	124.54	128.57
C6	124.58	134.97	127.05	131.50
C9	126.97	135.88	135.77	134.97
C2	139.19	136.99	139.29	135.88
C3	145.16	139.76	144.80	147.10
C5	156.20	141.38	155.78	163.01
C7	159.61	155.21	159.71	166.56
C20[a]		170.18	168.13 (broad)	172.08 (2C)
C23[a]		166.18	168.34 (broad)	170.14 (2C)
C21[a]		117.59	116.38	121.74 (2C)
C22[a]		115.22	115.59	120.71 (2C)

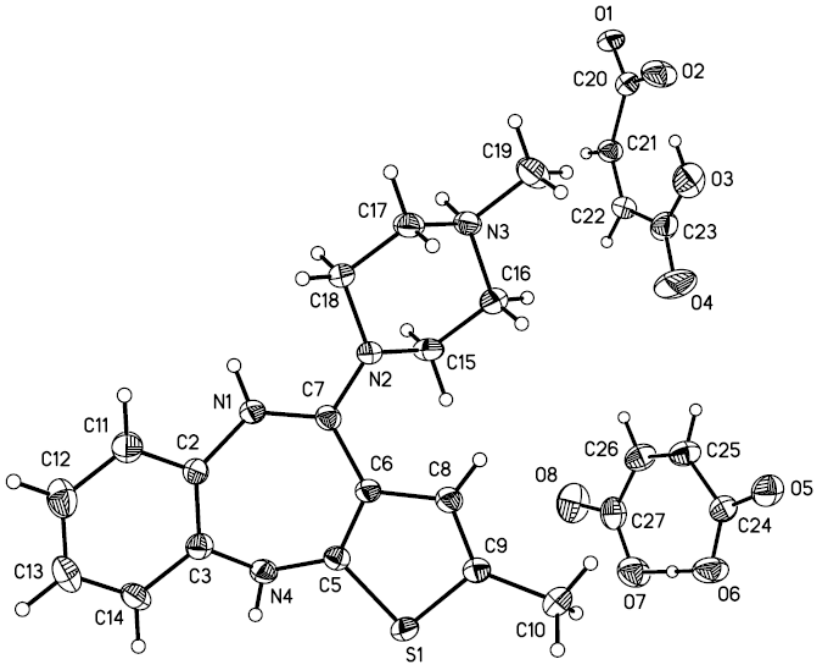
[a] Maleic acid.



(a)



(b)



(c)

Figure S1 ORTEP of (a) olanzapine base (b) olanzapinium monomaleate 1:1 salt and (c) olanzapinium dimaleate 1:2 salt.

Table S7 CHN analysis of the amorphous salts.

a. Amorphous Olanzapinium monomaleate 1:1 salt (molecular weight: 428.50 gm)

Atom	Calculated %	Experimental %
C	58.81	58.69
H	5.60	5.56
N	13.07	13.28

b. Amorphous Olanzapinium dimaleate 1:2 salt (molecular weight: 544.57 gm)

Atom	Calculated %	Experimental %
C	55.08	55.16
H	5.14	5.51
N	10.28	10.22

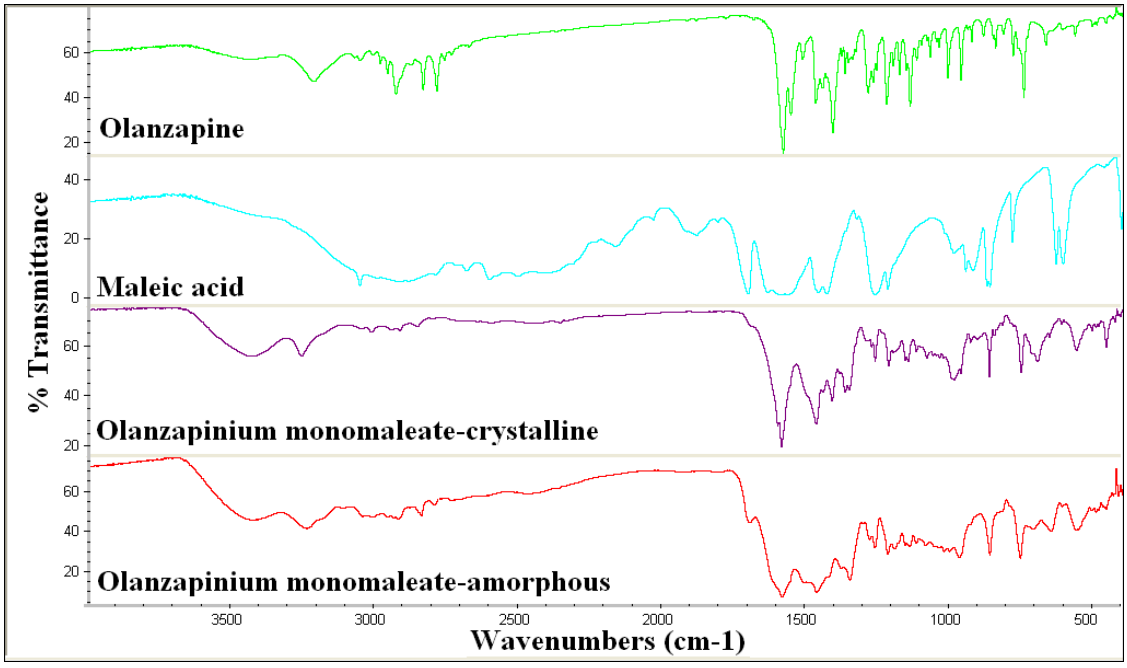


Figure S2 IR spectra of olanzapinium monomaleate 1:1 salt.

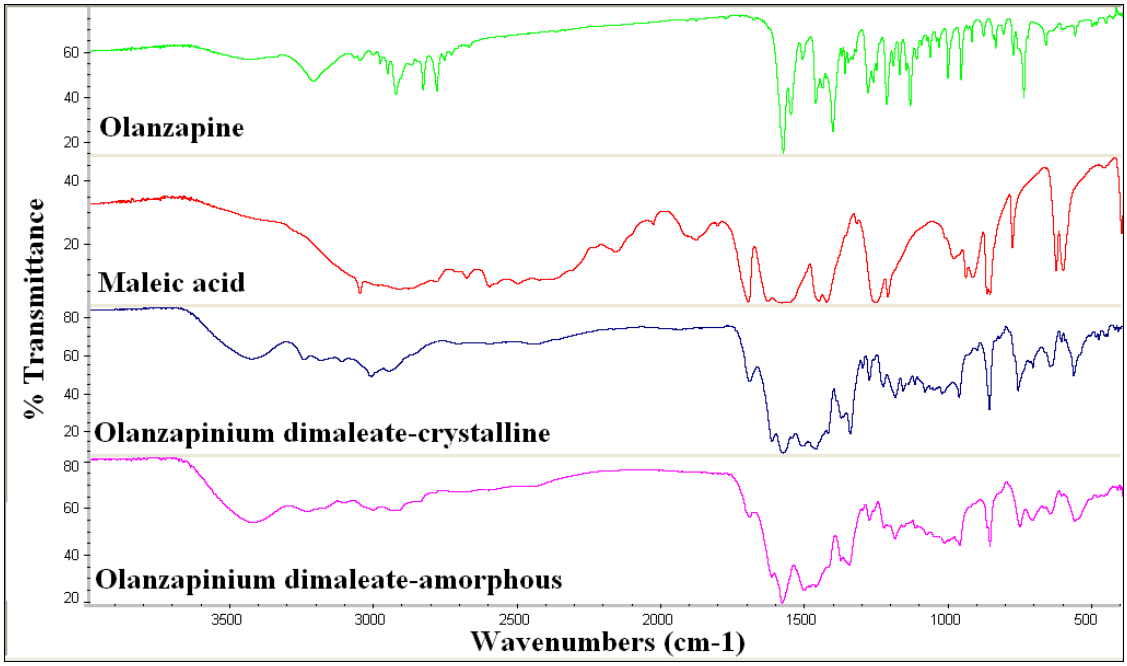


Figure S3 IR spectra olanzapinium dimaleate 1:2 salt.

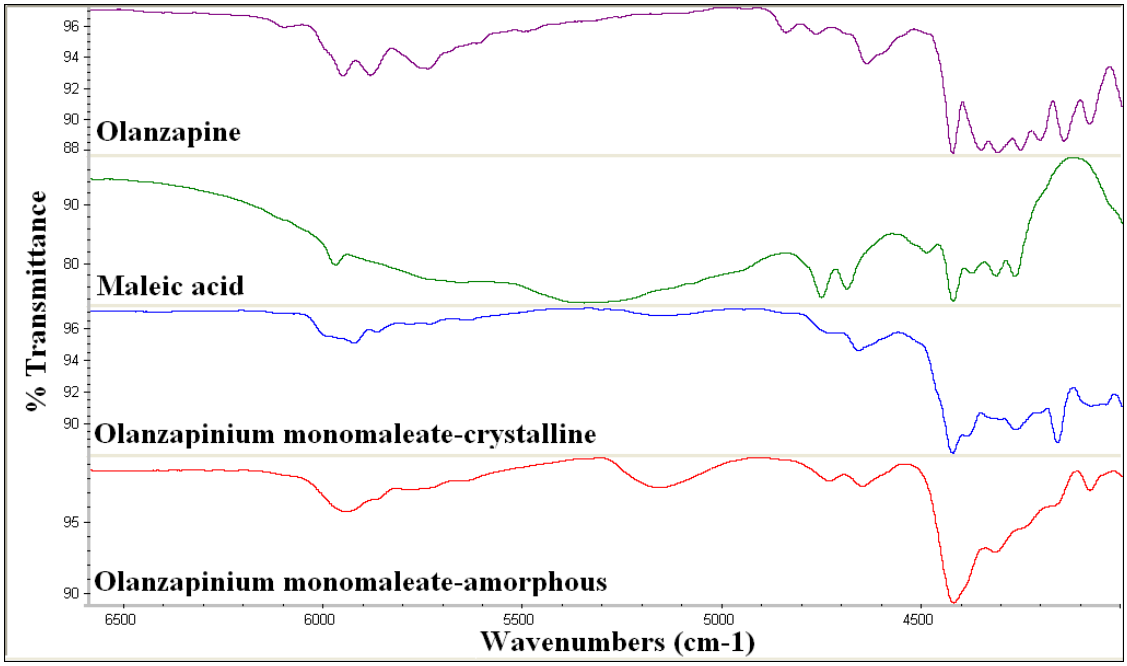


Figure S4 NIR spectra of olanzapinium monomaleate 1:1 salt.

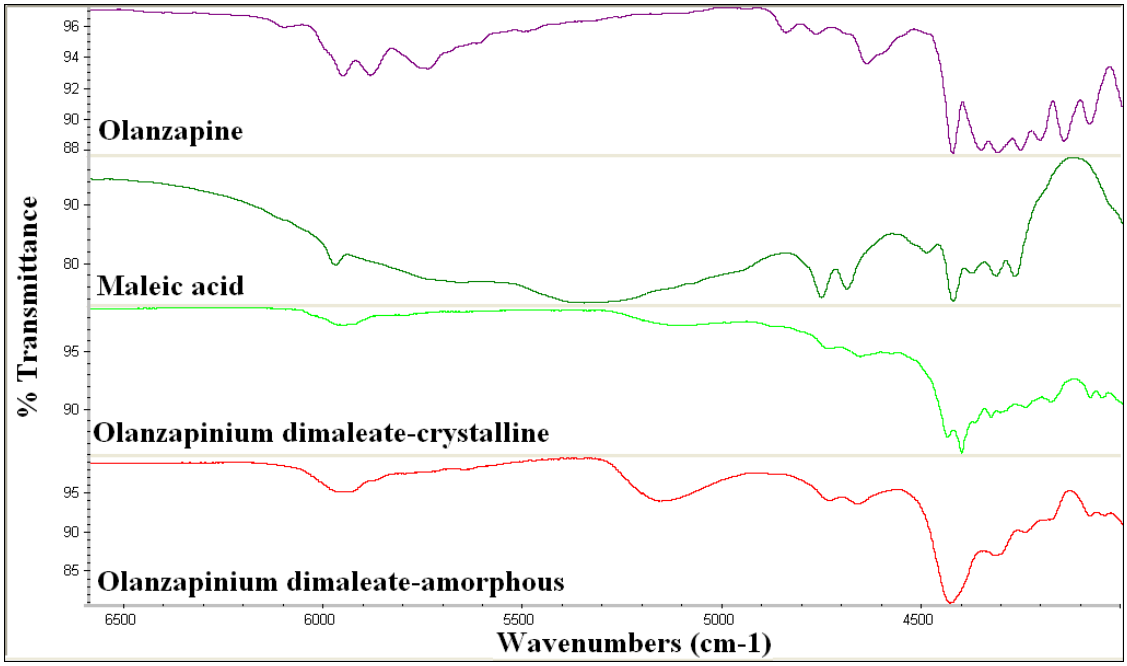


Figure S5 NIR spectra of olanzapinium dimaleate 1:2 salt.

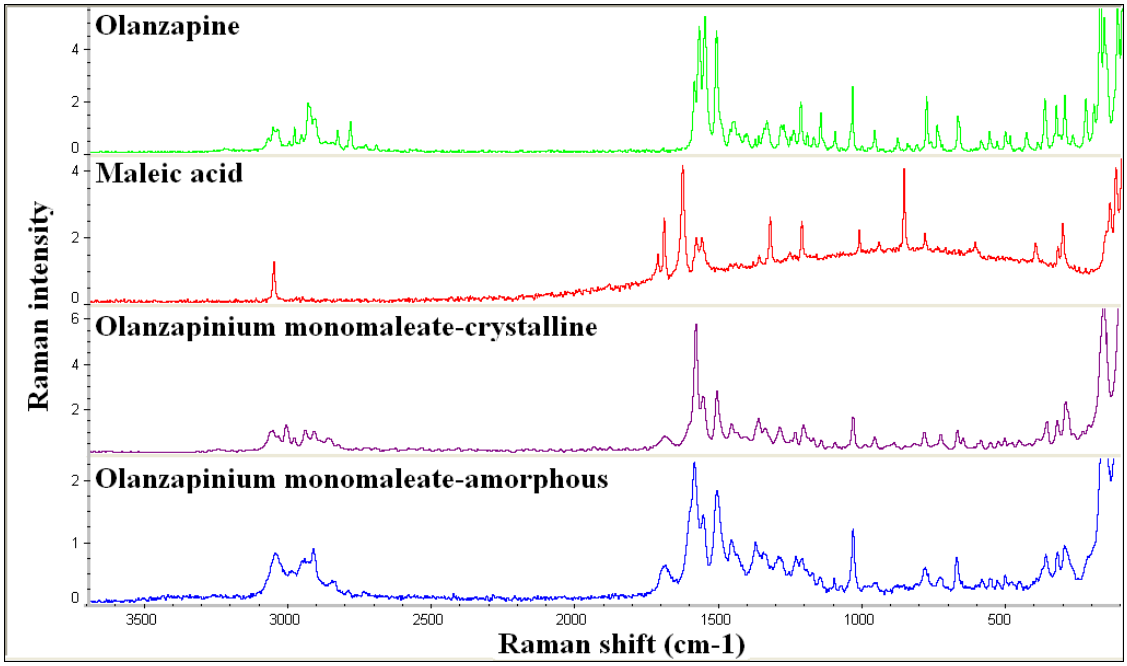


Figure S6 Raman spectra of olanzapinium monomaleate 1:1 salt.

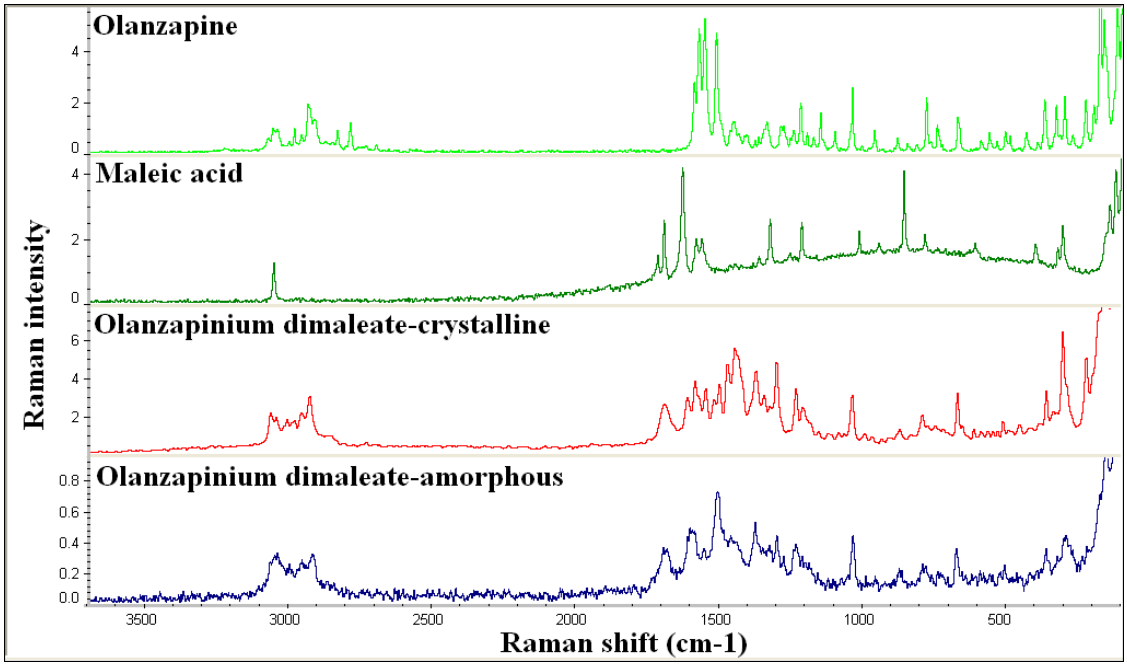


Figure S7 Raman spectra of olanzapinium dimaleate 1:2 salt.

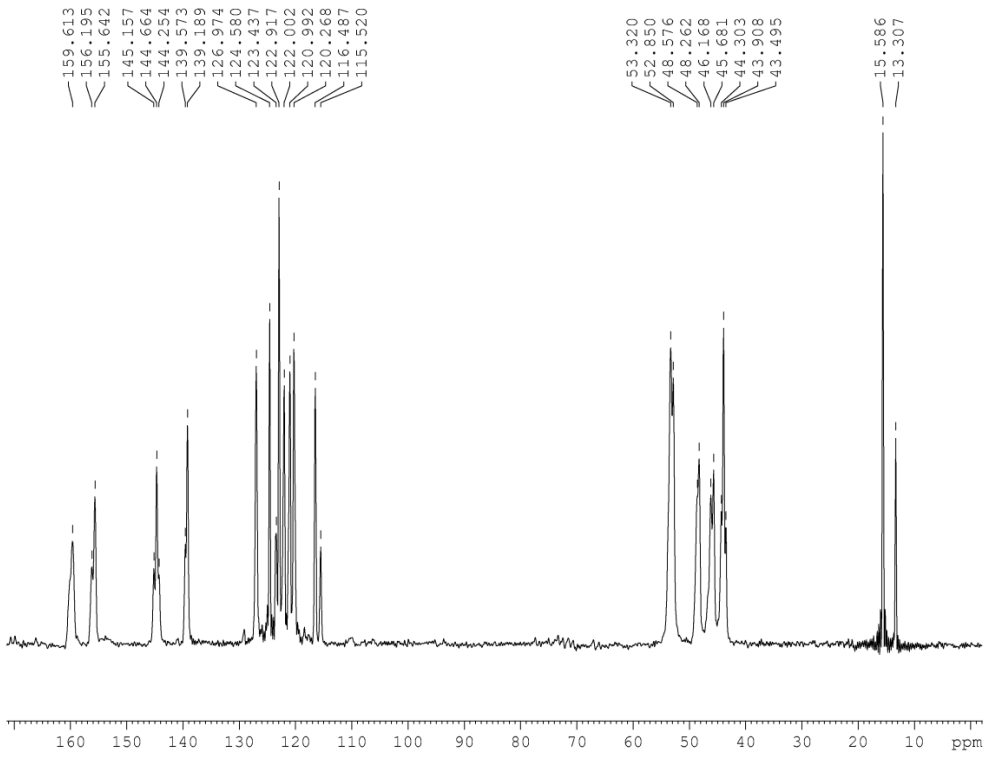


Figure S8 ss-NMR of olanzapine base.

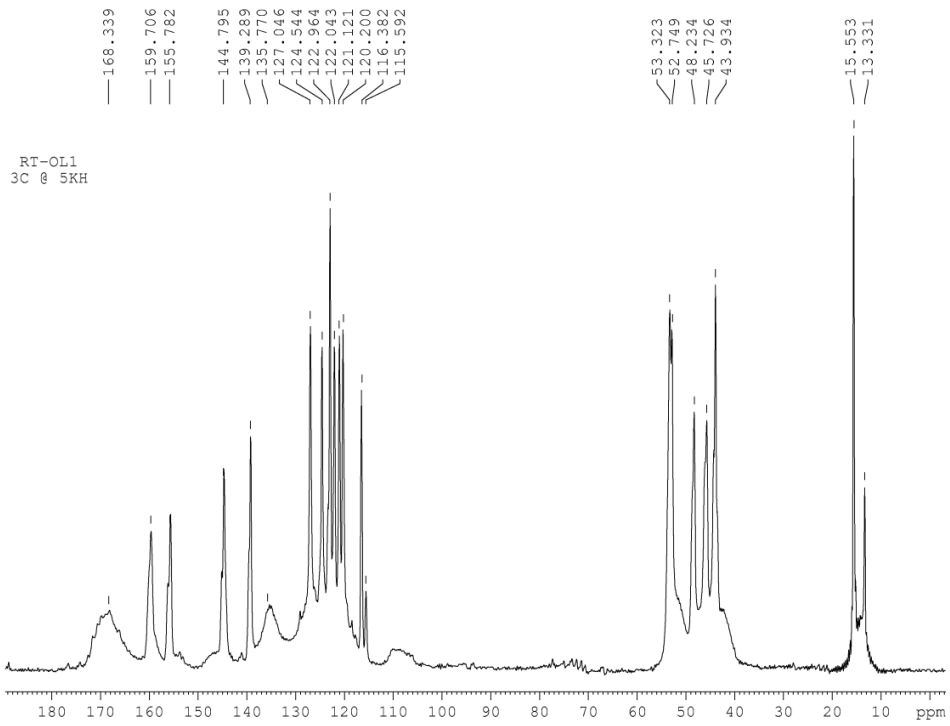


Figure S9 ss-NMR of amorphous olanzapinium monomaleate 1:1 salt.

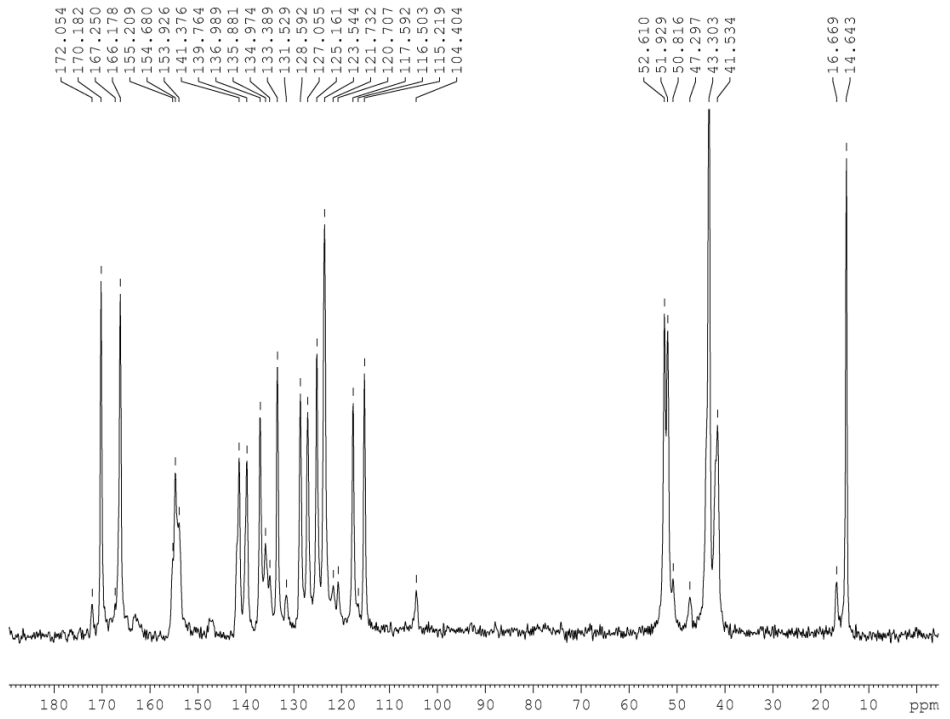


Figure S10 ss-NMR of crystalline olanzapinium monomaleate 1:1 salt.

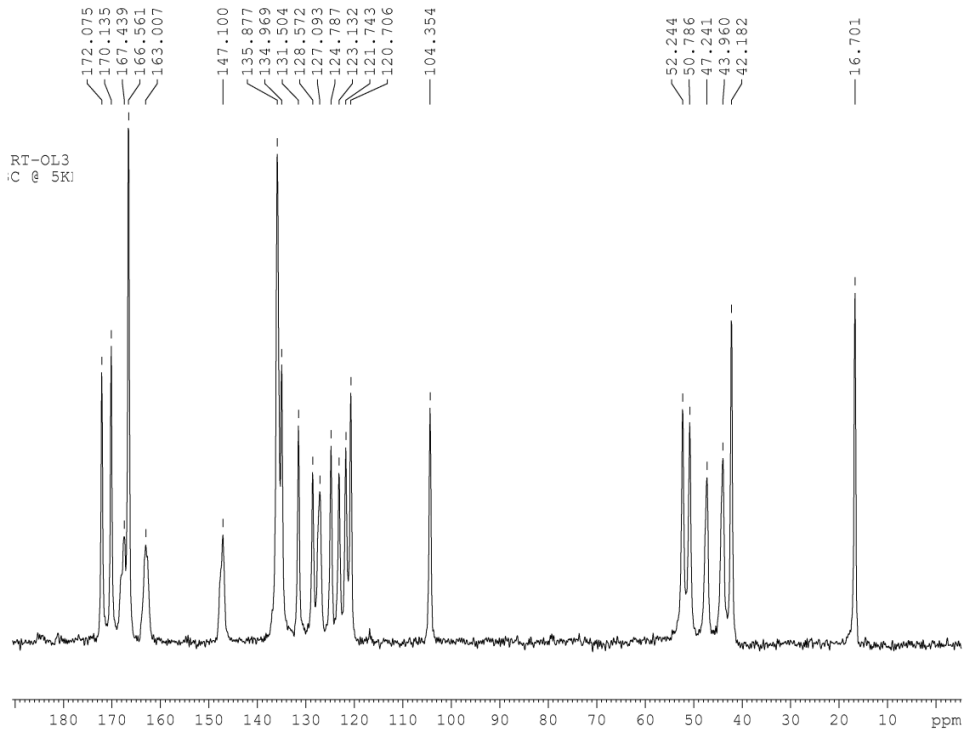


Figure S11 ss-NMR of crystalline olanzapinium dimaleate 1:2 salt.

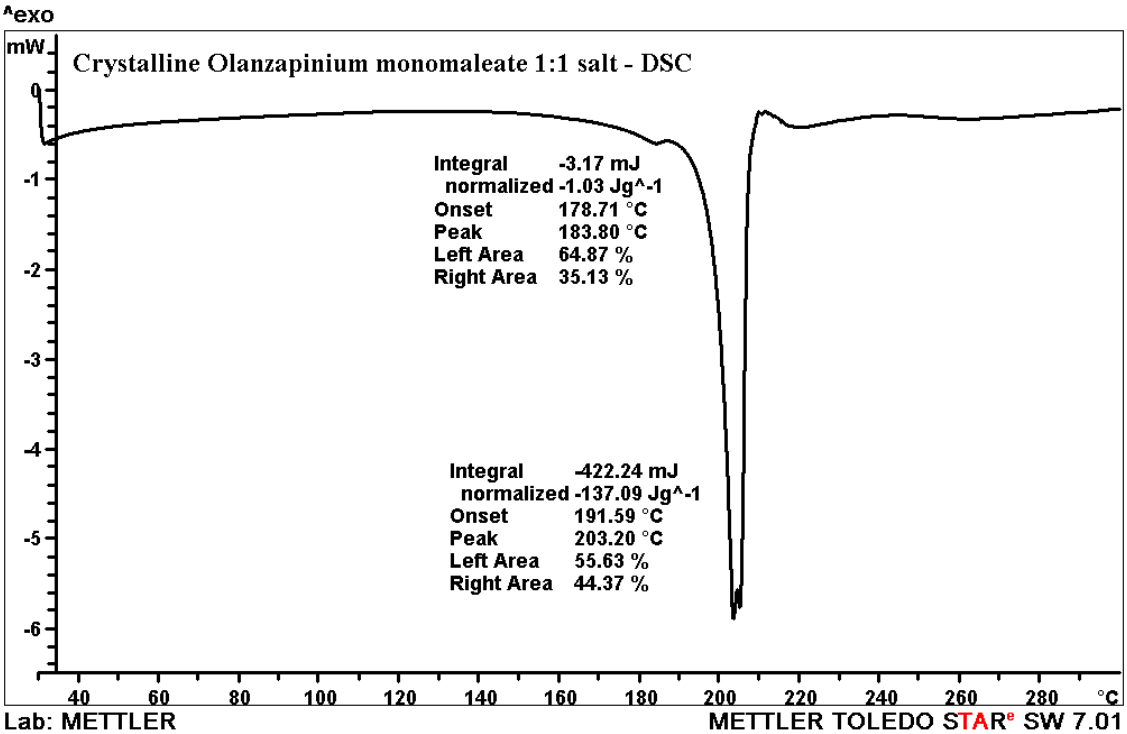


Figure S12 DSC of crystalline olanzapinium monomaleate 1:1 salt.

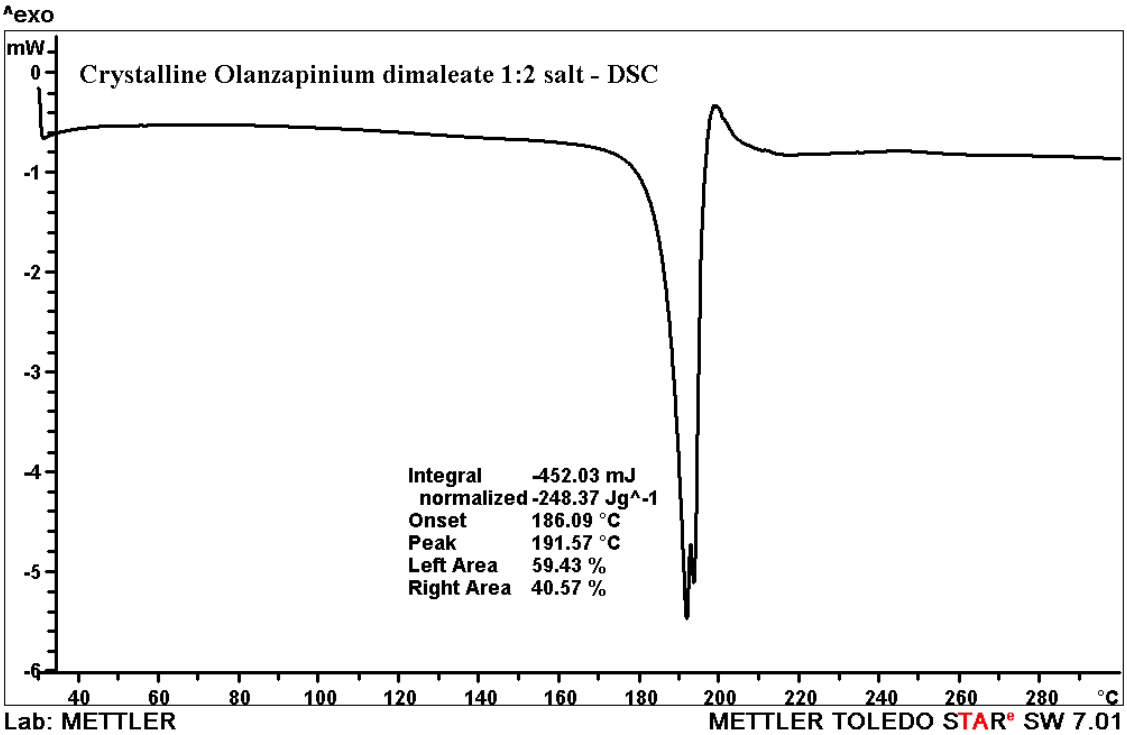


Figure S13 DSC of crystalline olanzapinium dimaleate 1:2 salt.

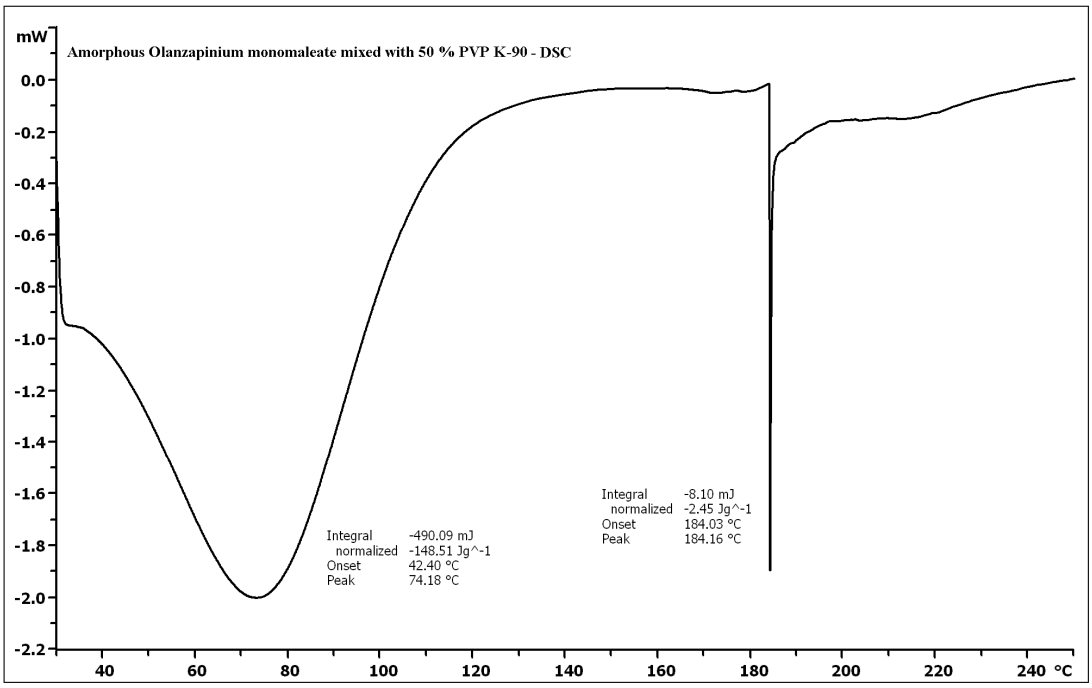


Figure S14 DSC of amorphous olanzapinium monomaleate after addition of 50% by weight PVP K–90 polymer the T_g from 60 °C (pure material) to 74 °C.

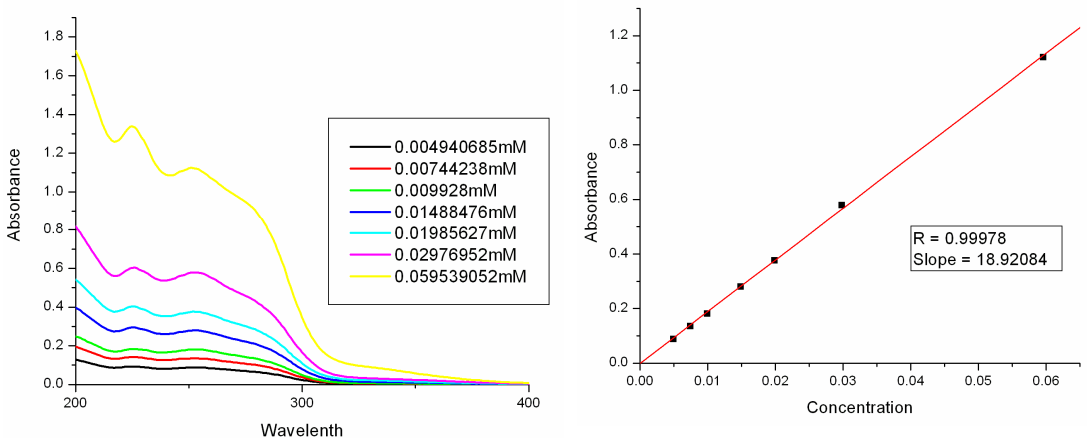


Figure S15 Absorption vs. wavelength and concentration vs. absorption curve for the standard solution of olanzapine free base in distilled water.

Preparation of the saturated solution of olanzapine base in distilled water:

Excess amount of OLN base was added to 8-10 mL of distilled water to make a saturated solution such that the undissolved solid was clearly visible. This slurry was stirred for 48 h, filtered material and the solution was diluted to get the absorbance value A within 1 in the UV-Vis spectrum. The XRPD of the residual precipitate was collected to check its solid-state nature.

Calculation:

Beer Lambert's Law: $A = \varepsilon c l$

where A is the absorbance, ε is coefficient of absorbance, c is the concentration and l is path length of the sample.

Olanzapine base in distilled water:

For the saturated solution A = 0.130 (20 times dilution) at λ = 253 nm, l = 1 cm, ε = 18.92084 /mmol/cm

Hence concentration of the saturated solution is **0.04293 mg/mL or 42.93 mg/L.**

The solubility of olanzapinium maleate salts were calculated in the same way.

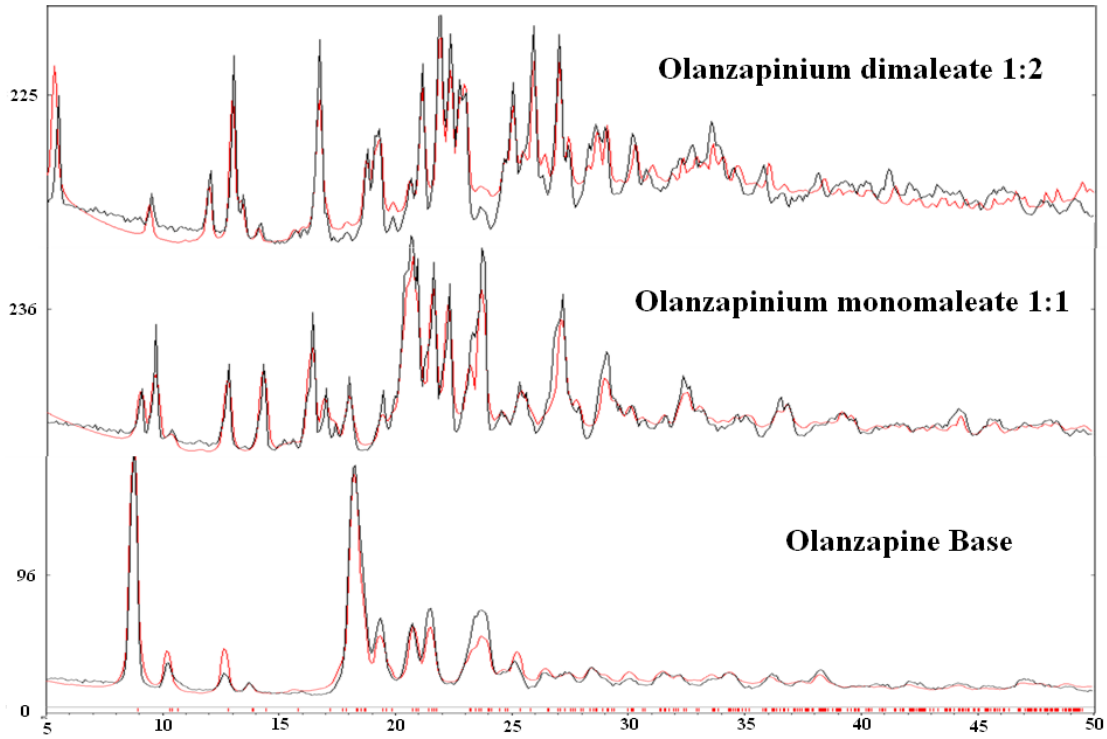


Figure S16 XRPD pattern of the olanzapine base and the crystalline salts after completion of the dissolution experiment and overlay of the calculated lines from the crystal structure confirm that the salts are stable during the dissolution experiment.

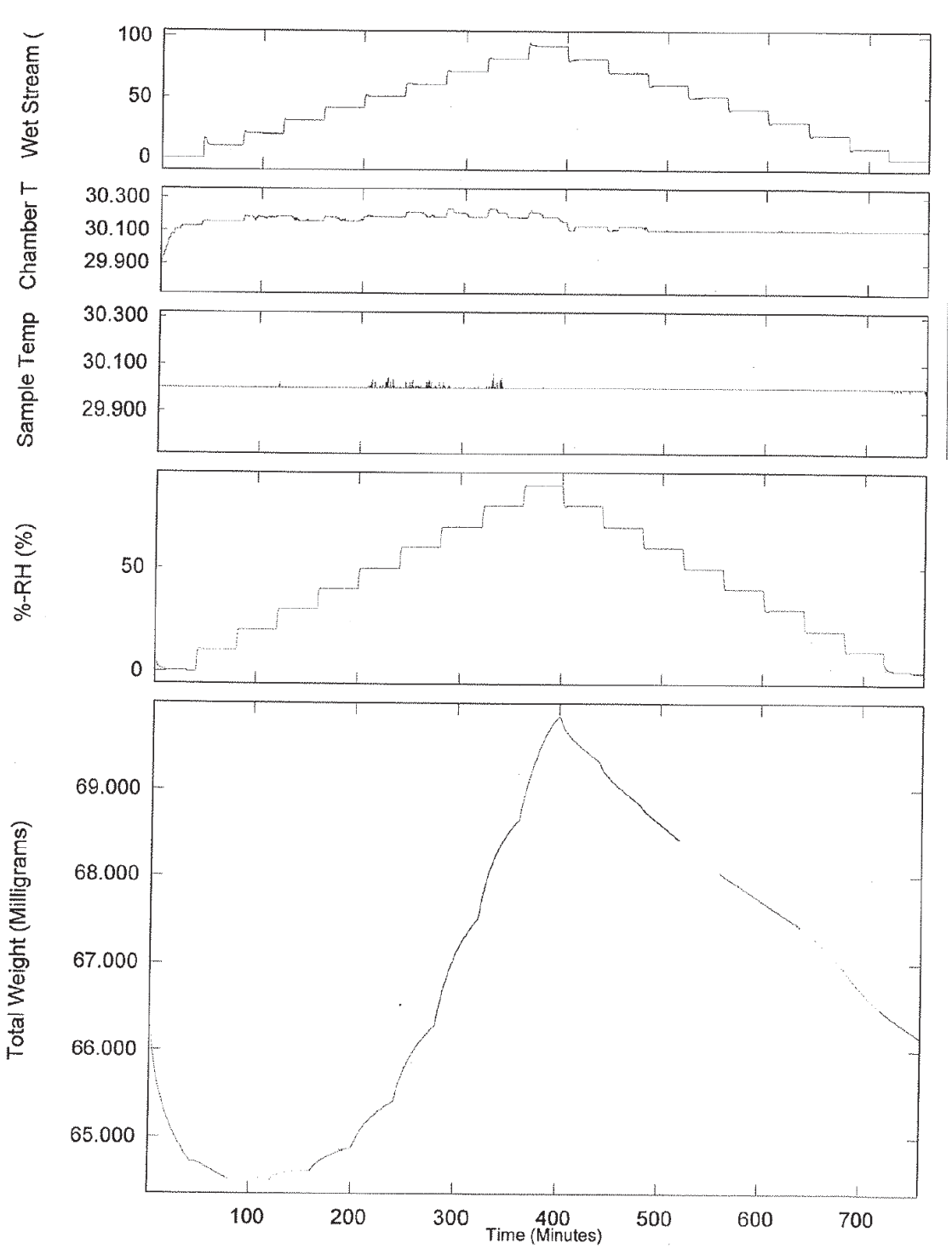


Figure S17 Dynamic vapour sorption (DVS) experimental conditions for amorphous OLN monomaleate.