Electronic Supplementary Information†

New polymorphs of curcumin†

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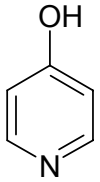
Crystallization conditions for Curcumin polymorphs

Pure Curcumin was purchased from Sigma-Aldrich and it was confirmed as Form 1 by X-ray powder diffraction. This material was used without further purification.

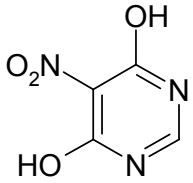
Table S1 Experimental techniques used to obtain polymorphs of curcumin.

Curcumin	Crystallization conditions	Time (days)
Form 1	Commercial sample or Sigma-Aldrich material. Good quality crystals were obtained from crystallization of 200 mg Curcumin in 10 mL isopropanol.	2-3
Form 2	(a) 200 mg (0.54 mmol) Curcumin and 52 mg (0.54 mmol) of 4-hydroxy pyridine were ground in mortar-pestle for 30 min after adding 5 drops of EtOH, and then kept for crystallization in 25 mL EtOH. The coformer 4-hydroxypyridine was obtained as precipitate at the bottom of the conical flask. Curcumin has low solubility in EtOH and crystallized faster and appeared as thick rod crystals.	3-4
	(b) 200 mg Curcumin was dissolved in 10 ml EtOH in 250 mL beaker and heated to make a supersaturated solution and then kept for crystallization in temperature controller refrigerator at 10 °C.	1-2

	(c) 200 mg Curcumin was dissolved in 5 mL DMSO in 25 ml beaker heated to make supersaturated solution and then kept at room temperature (30°C).	4-5
Form 3	100 mg Curcumin (0.27 mmol) and 42 mg (0.27 momol) of 4,6-dihydroxy-5-nitropyrimidine were ground in mortar-pestle for 30 min after adding 5 drops of EtOH, and then kept for crystallization in 10 mL EtOH. The coformer 4,6-dihydroxy-5-nitropyrimidine was obtained as precipitate at the bottom of the conical flask. Curcumin crystallized faster and appeared as starry aggregate of thin needle crystals. Form 3 crystals were difficult to obtain and sometimes what crystallized was Form 1.	2-3
Amorphous	100 mg Curcumin was melted at 190 °C and then immediately cooled to room temperature or dipped in ice to cool down to a glassy state.	Immed iate



4-Hydroxypyridine



4,6-dihydroxy-5-nitropyrimidine

Coformers used to crystallize Form 2 and 3 of Curcumin

Single crystal of polymorph 1 and 2 were of good quality and the data sets solved routinely to good accuracy. Crystals of polymorph 3 in thin needle morphology were the best quality we obtained for single crystal data collection, and the R-factor of this structure is slightly higher but accurate enough for structural comparison.

X-ray crystal structure solution and refinement

The crystal structure of Curcumin Form 1 was solved in monoclinic space group *P*2/n with one molecule in the asymmetric unit (*Z*' = 1). Strong intramolecular hydrogen bond (O4−H4A ··· O3, 1.51 Å, 2.441(2) Å, 155.7°) is present in the enol tautomer. Curcumin

molecules are aggregated into infinite chains linked through intermolecular phenolic OH and the enolic OH (O1−H1A··· O4, 2.28 Å, 2.904(2) Å, 119.8°) along the a-axis. Weak C−H···O interactions also play an important role in the overall molecular aggregation. There is a bifurcated C−H···O hydrogen bond involving phenolic O−H acceptor with aromatic hydrogen (C3−H3···O5: 2.58 Å, 3.544(2) Å, 149.6°) and olefinic hydrogen (C8−H8···O5: 2.54 Å, 3.528 (2) Å, 154.5°) donors.

The crystal structure of Curcumin Form 2 was solved in orthorhombic space group $Pca2_1$ with two molecules in the asymmetric unit ($Z' = 2$). Both the symmetry-independent molecules (A and B) have intramolecular O−H···O hydrogen bond in the enol tautomer. Molecule A (ball & stick model) forms intermolecular O−H···O hydrogen bond (O7−H7A···O9: 1.71 Å, 2.626(3) Å, 154.0°) with another molecule through enolic carbonyl and phenolic OH group along the c-axis. In contrast, Molecule B (capped stick model) forms an intermolecular O−H···O hydrogen bond (O1−H1A···O12: 2.23 Å, 2.834(3) Å, 119.0°). In addition B type molecules are connected intermolecularly by O−H···O hydrogen bond (O5−H5A···O1, 2.14 Å, 2.905(3) Å, 134.0°) between phenolic OH groups in a zigzag chain along the a-axis. The A molecules form O−H···O hydrogen bond (O11−H11A···O8: 1.96 Å, 2.896(3) Å, 159.0°) with the methoxy acceptor also along the a-axis. A and B type molecules are interconnected through bifurcated C−H···O interaction (C33−H33···O5: 2.32 Å, 3.288(3) Å, 148.0° and C31−H31···O5: 2.67 Å, 3.487(3) Å, 144.7°) from olefinic hydrogens to phenolic OH. There are C−H···O interactions from methoxy group of molecule B (C20−H20A···O11: 2.43 Å, 3.464(4) Å, 159.0° and C20−H20B···O2: 2.44 Å, 3.288(4) Å, 134.4°).

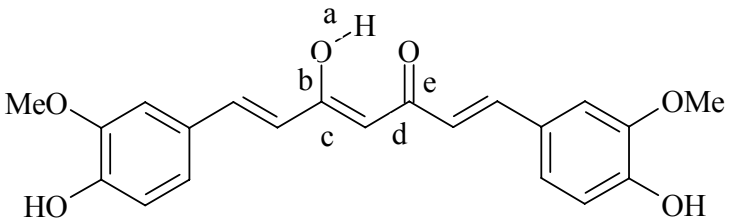
Form 3 crystal structure was solved in orthorhombic space group *Pbca* and with one molecule in the asymmetric unit. Strong intramolecular hydrogen bond (O4−H4A···O3: 1.59 Å, 2.490 (6) Å, 149.6°) is present in the enol tautomer. Form 3 molecules aggregate intermolecularly into infinite chains through phenolic OH and carbonyl O hydrogen bond (O1−H1···O3: 1.69 Å, 2.666(5) Å, 167.9°) along the a-axis. In addition a weaker O−H···O hydrogen bond (O5−H5A···O2: 2.17 Å, 2.975(6) Å, 137.8°) exists between phenolic OH and methoxy group along the c-axis. There is C−H···O interaction (C20−H20B···O4: 2.41 Å, 3.192 (7) Å, 127.6°) from methoxy hydrogen to hydroxyl acceptor.

Table S2 Crystallographic parameters of Curcumin polymorphs.

Curcumin	Form 1	Form 2	Form 3
Empirical Formula	C_{21} H_{20} O_6	C_{21} H_{20} O_6	C_{21} H_{20} O_6
Formula weight	368.37	368.37	368.37
Crystal system	Monoclinic	Orthorhombic	Orthorhombic
Space group	*P*2/*n*	*P*ca2$_1$	*Pb*ca
T (K)	100(2)	100(2)	100(2)
a (Å)	12.5676(11)	35.417(3)	12.536(3)
b (Å)	7.0425(6)	7.7792(7)	7.9916(17)
c (Å)	19.9582(18)	12.6482(11)	34.462(7)
α (°)	90	90	90
β (°)	94.987(1)	90	90
γ(°)	90	90	90
V (Å^3)	1759.8(3)	3484.7(5)	3452.3(13)
D_{calcd} (g cm^{-3})	1.390	1.404	1.417
μ (mm^{-1})	0.102	0.103	0.104
θ range	3.07 to 26.02	2.30 to 25.89	2.80 to 26.31
Z/*Z*′	4/1	8/2	8/1
Range *h*	–15 to +15	–43 to +43	–15 to +15
Range *k*	–8 to +8	–9 to +9	–9 to +9
Range *l*	–24 to +24	–15 to +15	–43 to +43
Reflections collected	17534	34779	8888
Observed reflections	3467	6854	3510
Total reflections	3107	6199	1127
R(int)	0.0308	0.0497	0.1808
R_1 [$I > 2\ \sigma(I)$]	0.0435	0.0513	0.0893
*w*R$_2$ (all)	0.1163	0.1218	0.1681

Goodness-of-fit	1.054	1.083	0.930
C_k (%)	72.5	72.6	72.7
Diffractometer	CCD-CAD-4	CCD-CAD-4	Oxford-CCD

Table S3 Comparison of bond lengths to estimate extent of symmetrization in keto-enol fragment.[a]



Bond type	a (O–H in Å)	b (C–O in Å)	e (C=O in Å)	c (C=C in Å)	d (C–C in Å)	Symmetry/ asymmetry
Form 1	1.07	1.30	1.30	1.40	1.38	Sym
Form 2 A	0.94	1.31	1.27	1.37	1.42	Asym
Form 2 B	0.95	1.33	1.27	1.37	1.41	Asym
Form 3	0.83	1.33	1.28	1.36	1.43	Asym

[a] Chemical symmetrization is defined as near equality of C–C and C–O bond lengths in keto-enol fragment. See F. H. Herbstein, B. B. Iverson, M. Kapon, F. K. Larson, G. K. H. Madsen and G. M. Reisner, *Acta Cryst.*, 1999, **B55**, 767.

Table S4 Hydrogen bonds in crystal structures (neutron-normalized distance).

Crystal Form	Interaction	H···A /Å	D···A /Å	∠D–H···A /º	Symmetry code
Form 1	O1−H1A···O2	2.14	2.667(2)	111.5	Intramolecular
	O1−H1A···O4	2.28	2.904(2)	119.8	-1+x,y,z
	O4−H4A···O3	1.51	2.441(2)	155.7	Intramolecular
	O5−H5A···O6	2.23	2.695(2)	107.4	Intramolecular
	O5−H5A···O3	1.89	2.793(2)	150.1	1/2+x,-y,-1/2+z

	C7−H7···O3	2.37	2.779(2)	100.0	Intramolecular
	C3−H3···O5	2.58	3.544(2)	149.6	½-x,y,1/2-z
	C8−H8···O5	2.54	3.528 (2)	154.5	½-x,y,1/2-z
	C7−H7···O6	2.38	3.449(2)	166.9	-1/2+x,-y,1/2+z
	C19−H19···O1	2.46	3.492(2)	157.3	-x,-y,1-z
	C20−H20A···O3	2.49	3.557(2)	166.5	1-x,-y,1-z
Form 2	O1−H1A···O2	2.02	2.655 (3)	120.0	Intramolecular
	O1−H1A···O12	2.23	2.834(3)	119.0	-1/2+x,1-y,z
	O3−H3A···O4	1.58	2.498(3)	154.0	Intramolecular
	O5−H5A···O6	2.07	2.646(3)	115.0	Intramolecular
	O5−H5A···O1	2.14	2.905(3)	134.0	1/2+x, -y,z
	O7−H7A···O9	1.71	2.626(3)	154.0	-x,2-y, -1/2+z
	O10−H10A···O9	1.64	2.528(3)	147.0	Intramolecular
	O11−H11A···O12	2.27	2.711(3)	106.0	Intramolecular
	O11−H11A···O8	1.96	2.896(3)	159.0	1/2+x,1-y,z
	C20−H20A···O11	2.43	3.464(4)	159.0	symmetry independent molecules
	C20−H20B···O2	2.44	3.291(4)	135.0	1/2+x, -y,z
	C33−H33···O5	2.32	3.289(3)	147.8	3/2-x,-1+y,-1/2+z
	C41−H41B···O4	2.38	3.032(3)	116.6	3/2-x,y,1/2+z
Form 3	O1−H1···O3	1.69	2.666(5)	167.9	1/2+x,3/2-y,1-z
	O4−H4A···O3	1.59	2.490(6)	149.6	Intramolecular
	O5−H5A···O6	1.99	2.685(6)	124.8	Intramolecular
	O5−H5A···O2	2.17	2.975(6)	137.8	x,1/2-y,1/2+z
	C13−H13···O4	2.34	2.754(8)	100.7	Intramolecular
	C20−H20B···O4	2.41	3.192(7)	127.6	1-x,-1/2+y,3/2-z

Table S5 FT-IR vibrational modes frequency (cm^{-1}) of three polymorphs and amorphous phase.

	O−H	C=O	Aromatic C=C	Phenol C−O	Enol C−O
Form 1	3510.9	1627.5	1602.6	1429.0	1281.2
Form 2	3401.2 (broad), 3254.1	1651.6, 1626.7	1588.1, 1601.4	1427.3	1282.6, 1263.5
Form 3	3440.9 (broad)	1626.8	1587.3	1416.7	1262.1
Amorphous	3440.6 (broad)	1629.9	1588.4	1428.5	1280.7, 1262.8

Table S6 FT-Raman vibrational modes frequency (cm^{-1}) of three polymorphs and amorphous phase.

	C=O	Aromatic C=C	Phenol C−O	Enol C−O
Form 1	1626.2	1600.4	1430.2	1249.3
Form 2	1638.9	1591.1, 1602.3	1415.6	1233.1
Form 3	1637.9	1591.4	1415.2	1234.4
Amorphous	1630.5	1599.3	1428.8	1243.2

Table S7 ^{13}C NMR chemical shifts of Curcumin three polymorphs and amorphous phase in the solid-state and solution spectrum.

^{13}C peak	Form 1	Form 2	Form 3	Amorphous	Curcumin (d^6 DMSO)
1, 17	156.753, 157.703	163.589 152.618	163.557, 159.906, 156.038	157.564	153.203, 154.546
2, 18	146.910	144.812	145.904	146.782	145.953, 145.614
3, 19	106.949	103.351	102.772	103.140	116.17
4, 14	128.283, 127.732	127.111	127.397	126.263	128.341

5, 15	108.614, 107.293	104.028	114.114	106.522 (broad)	126.297
6, 16	113.437, 113.023	113.630 109.387	116.668	113.995	116.477
7, 13	139.105, 138.649	133.519	139.030	139.218	131.548
8, 12	123.664, 121.338	120.308	125.190	122.294	121.127, 120.907
9, 11	184.496, 182.223	193.409, 187.572 (broad), 183.102	188.074, 184.673, 180.771, 177.530	177.237, 189.242 (broad)	188.417
10	97.540	96.235 (broad)	93.123, 97.851	97.326	106.063
20, 21	55.576, 53.693	60.812	56.150, 54.592	53.884	60.898

Table S8 Melting Point (onset, peak), Enthalpy of fusion[a] (ΔH_{fus}).

Curcumin	Form 1	Form 2	Form 3
T_m (onset/peak)	177.57	171.95	168.29
(°C)	181.42	175.12	172.85
H_f (kJ mol^{-1})	37.19	34.98	31.31

[a] Enthalpy of Fusion values indicate the stability order as Form 1 (most stable) > Form 2 > Form 3 > Amorphous. The values for the amorphous phase are not mentioned because it transformed to Form 1 during heating.

Dissolution and solubility experiments

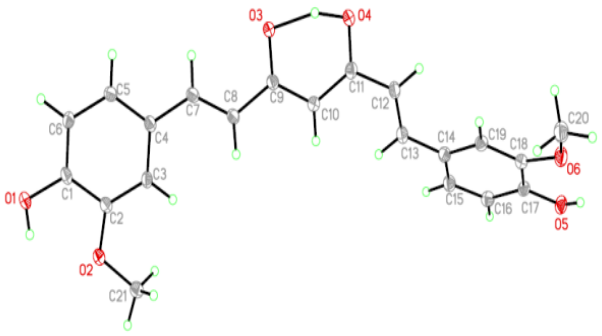
Intrinsic dissolution rate (IDR) and solubility measurements were carried out on a USP-certified Electrolab TDT-08 L Dissolution Tester. A calibration curve was obtained for Form 1, Form 2 and amorphous phase of Curcumin by plotting absorbance vs. concentration curve of UV-Vis spectra for known concentration solutions in 40% EtOH-water medium. The mixed solvent system was selected because curcumin has high

solubility in this medium. The slope of the plot gave the molar extinction coefficient (ε) by using the Beer-Lambert's law. The ε value for Form 1 = 46.21 /mM cm, Form 2 = 43.99 /mM cm, and Amorphous = 38.75 /mM cm. To obtain the equilibrium solubility, 100 mg of each polymorphs of Curcumin was stirred for 24 h in 5 mL 40% EtOH-water medium at 37 °C, and the absorbance was measured at 430 nm. The concentration of the saturated solution was calculated at 24 h, which is called as the Equilibrium solubility of that polymorph. The Apparent solubility is more appropriate for Form 2 and Amorphous phase because they were found to transform to the stable Form 1 under the solubility measurement conditions. The Apparent Solubility of a metastable polymorph is calculated using the equation

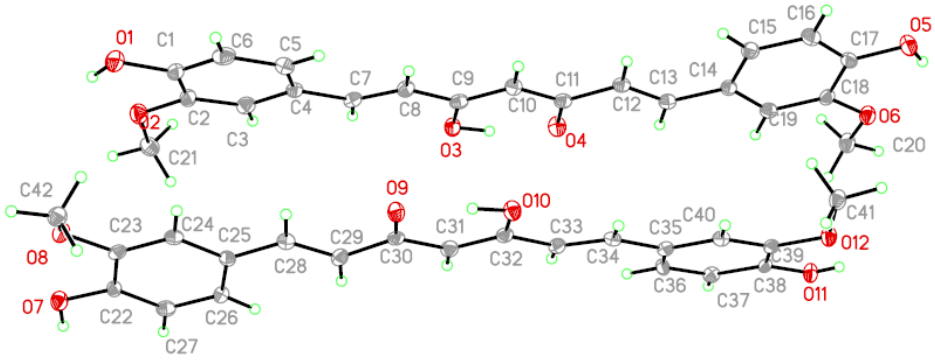
$$\text{Solubility}_{\text{metastable}} = \text{Solubility}_{\text{stable}} \, (\text{IDR}_{\text{metastable}} / \text{IDR}_{\text{stable}})$$

See (a) M. Otsuka, R. Teraoka and Y. Matsuda, Chem. Pharm. Bull., 1991, 39, 2667; (b) V. M. Rao, R. Sanghvi and H. Zhu, in *Developing Solid Oral Dosage Forms, Pharmaceutical Theory and Practice*, Y. Qiu, Y. Chen and G. G. Z. Zhang (Eds.), 1st Ed., 2009, Burlington: Elsevier, pp. 3-24.

For IDR experiments, 100 mg of each polymorph was taken in the intrinsic attachment and compressed to a 0.5 cm^2 pellet using a hydraulic press at a pressure of 2.5 ton/$inch^2$ for 2 min. The pellet was compressed to provide a flat surface at one end and the other end was sealed. Then the pellet was dipped into 900 mL 40% EtOH-water medium at 37 °C with the paddle rotating at 150 rpm. At regular interval of 10 minutes, 5 mL of the dissolution medium was withdrawn and replaced by an equal volume of fresh medium to maintain a constant volume. Samples were filtered through 0.2 μm nylon filter and assayed for drug content spectrophotometrically at 430 nm. The amount of drug dissolved in each time interval was calculated using the calibration curve. The dissolution rates for the three polymorphs of Curcumin were computed from their IDR values.



(a)



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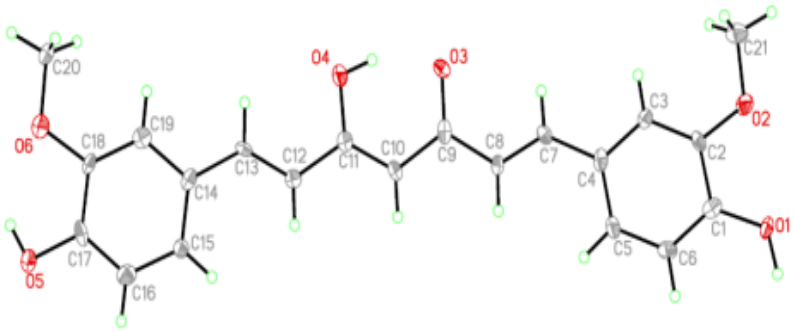

(c)

Fig. S1 ORTEP diagram of Curcumin (a) Form 1, (b) Form 2 and (c) Form 3 at 35% probability of electron density for thermal ellipsoids. There are two symmetry-independent molecules in Form 2.

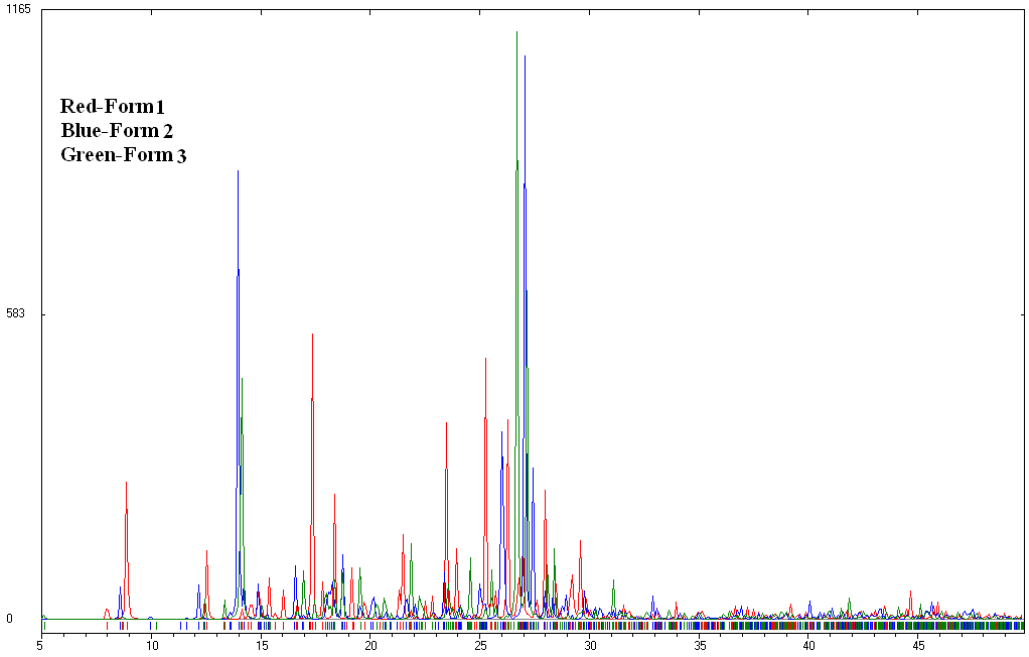

Fig. S2 Overlay of calculated X-ray lines for Form 1, 2 and 3 from the crystal structure.

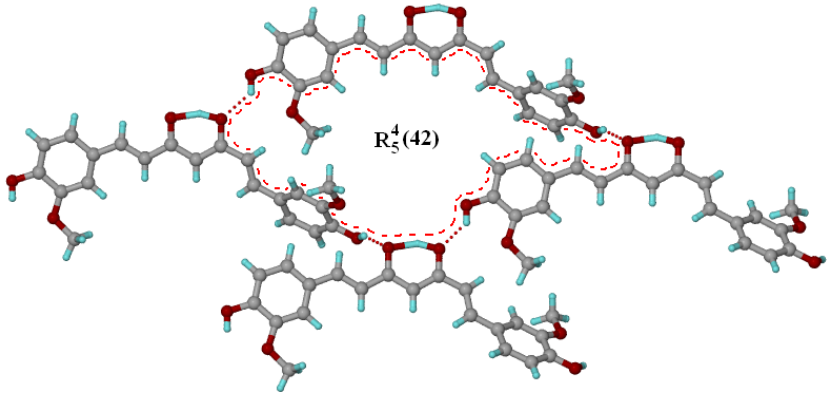

Fig. S3 Hydrogen bond ring of $R^4_5(42)$ graph set notation in the crystal structure of Form 1. Such a ring motif is absent in Form 2 and 3.

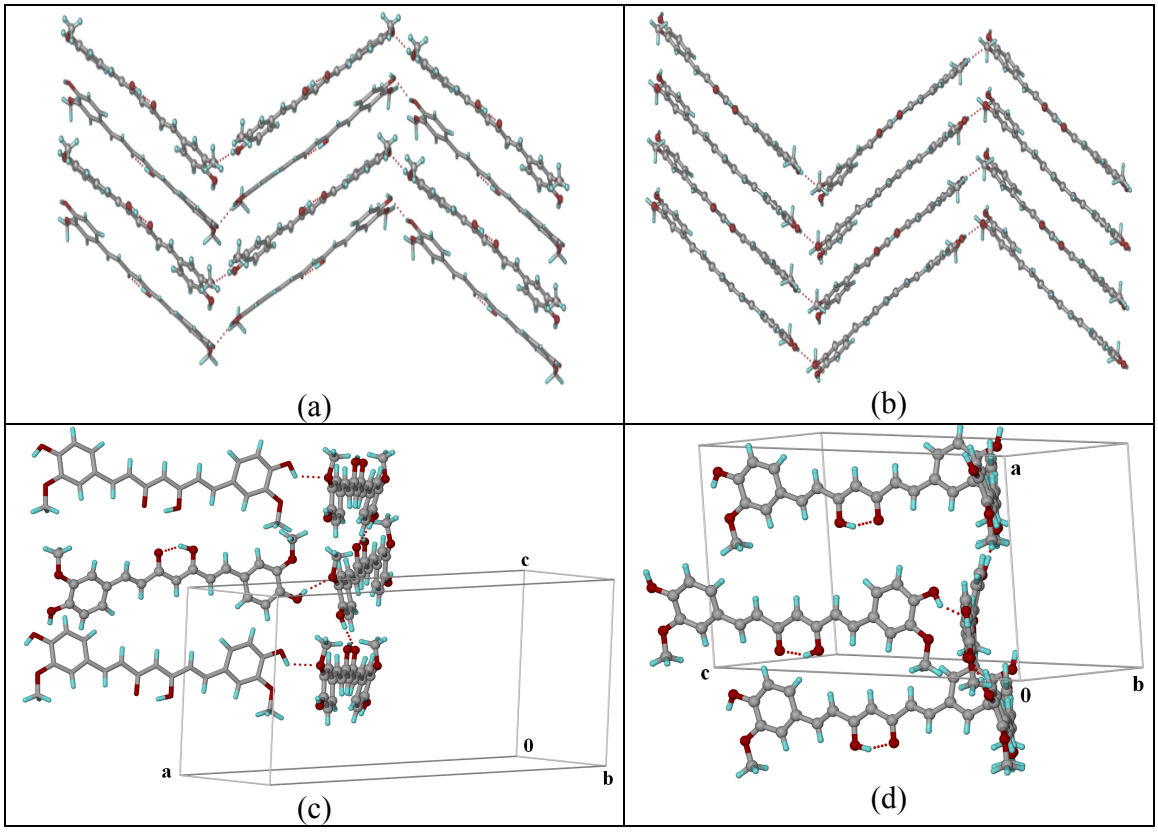

Fig. S4 Similarities and subtle differences in the molecular packing of Curcumin Form 2 and 3. (a) O−H···O(OMe) hydrogen bond of symmetry-independent molecules along [100] in Form 2. (b) Chain of O−H···O(OMe) hydrogen bonds along [001] in Form 3. (c) A cluster of six molecules in Form 2. (d) Similar cluster in Form 3. Note that the keto-enol group orientation for the middle molecule is different. The b-axis of the two orthorhombic unit cells are similar and a- and c-axes are interchanged (dimensions are approximately equal).

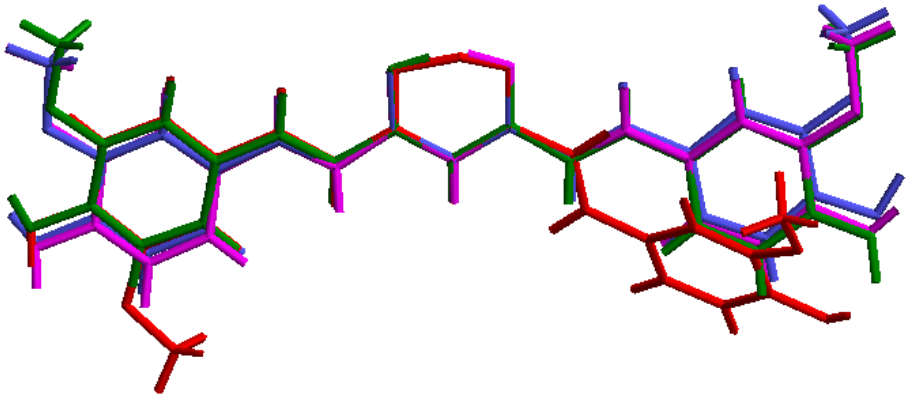

Fig. S5 Molecular overlay diagram for three crystalline polymorphs, Form 1 (red), Form 2 (blue and magenta), and Form 3 (green). The RMSD for molecular overlay are: Form 1 and 2 (2.00), Form 1 and 3 (1.99), Form 2 and 3 (0.46).

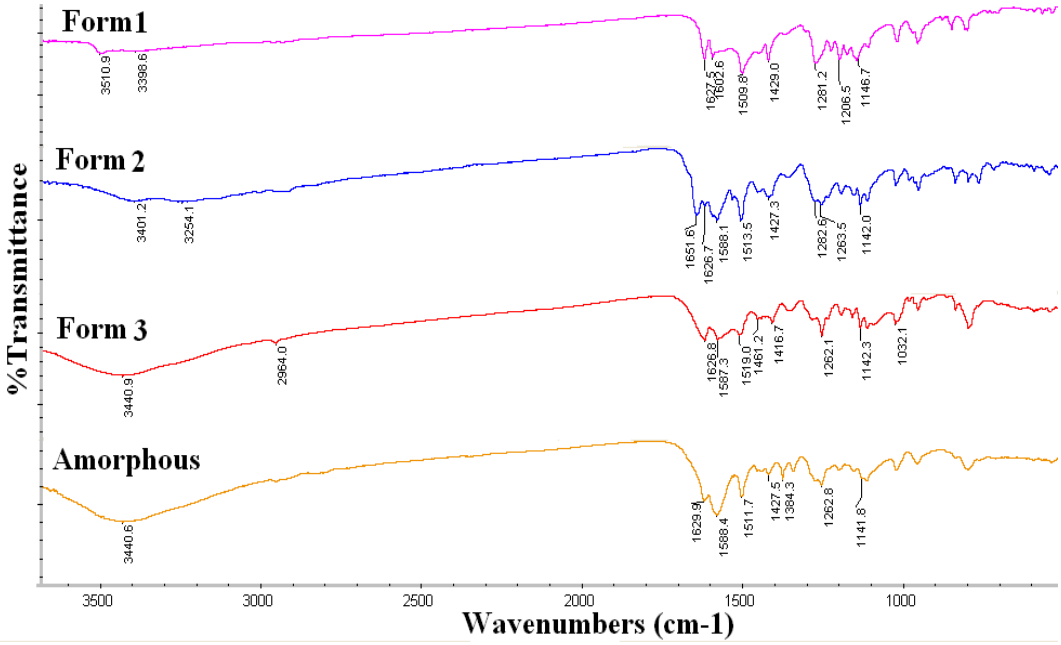

Fig. S6 FT-IR spectra comparison of Curcumin three polymorphs and amorphous phase.

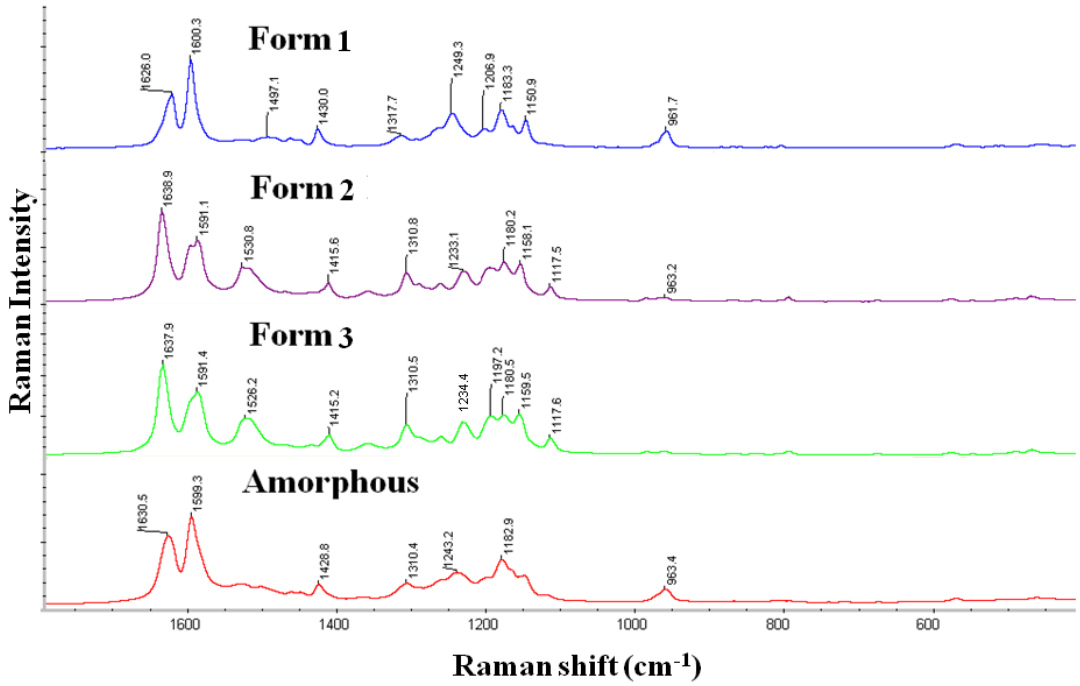

Fig. S7 FT-Raman spectra comparison of Curcumin three polymorphs and amorphous phase.

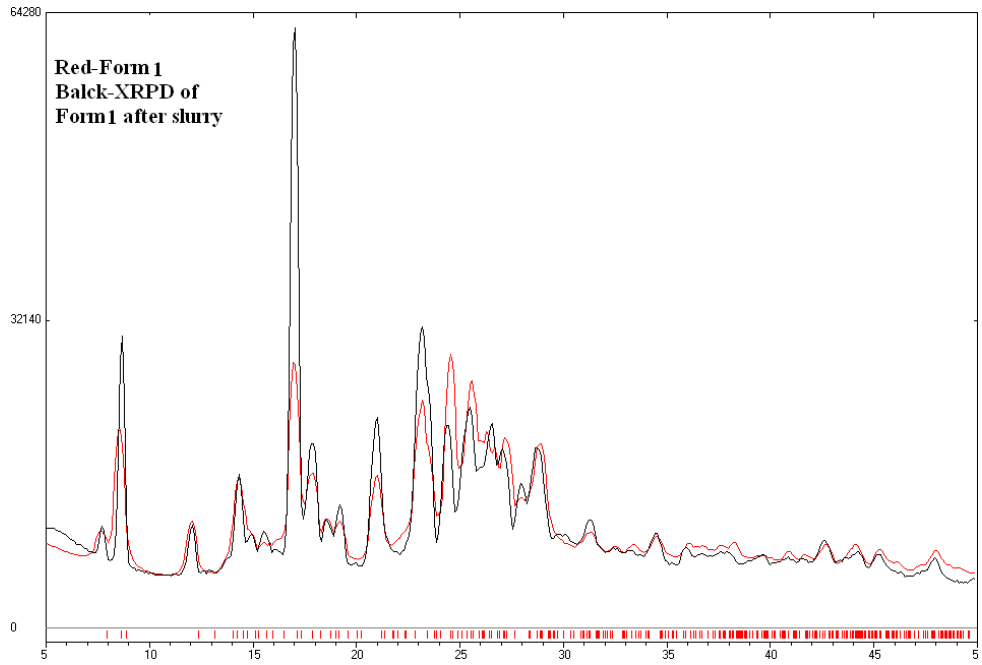

Fig. S8 XRPD of Form 1 after slurry grinding (black) with calculated XRD lines from the crystal structure (red) shows excellent match.

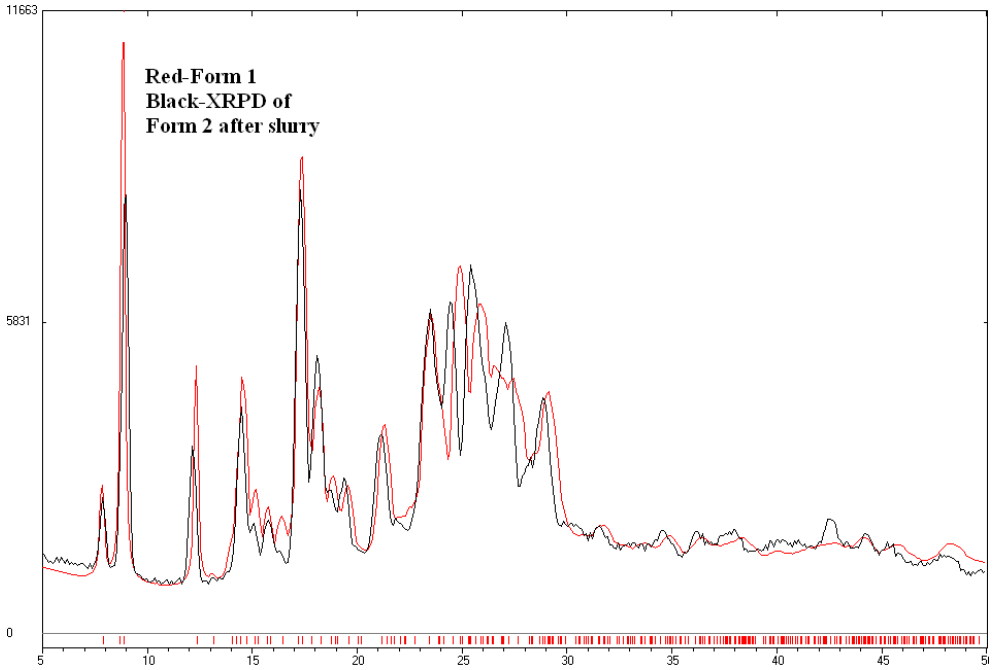

Fig. S9 XRPD of Form 2 after slurry grinding (black) with the calculated XRD lines from the crystal structure shows that it has transformed to Form 1.

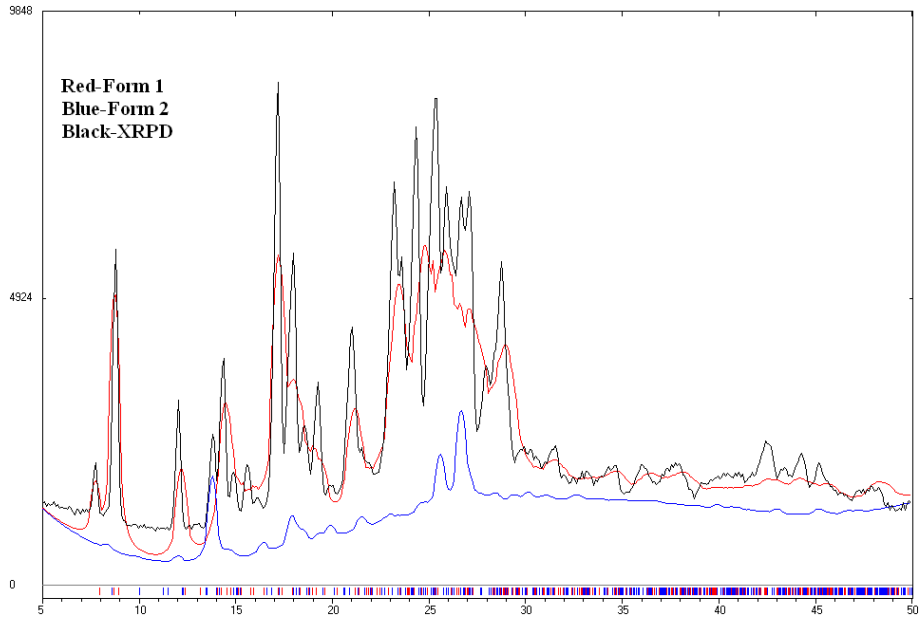

Fig. S10 XRPD of the amorphous solid after 24 h slurry grinding (black) matched with the calculated XRD lines of Form 1 (red) and Form 2 (blue) of Curcumin. Rietveld refinement gave an estimate of 90% Form 1 and 10% Form 2 in the sample.

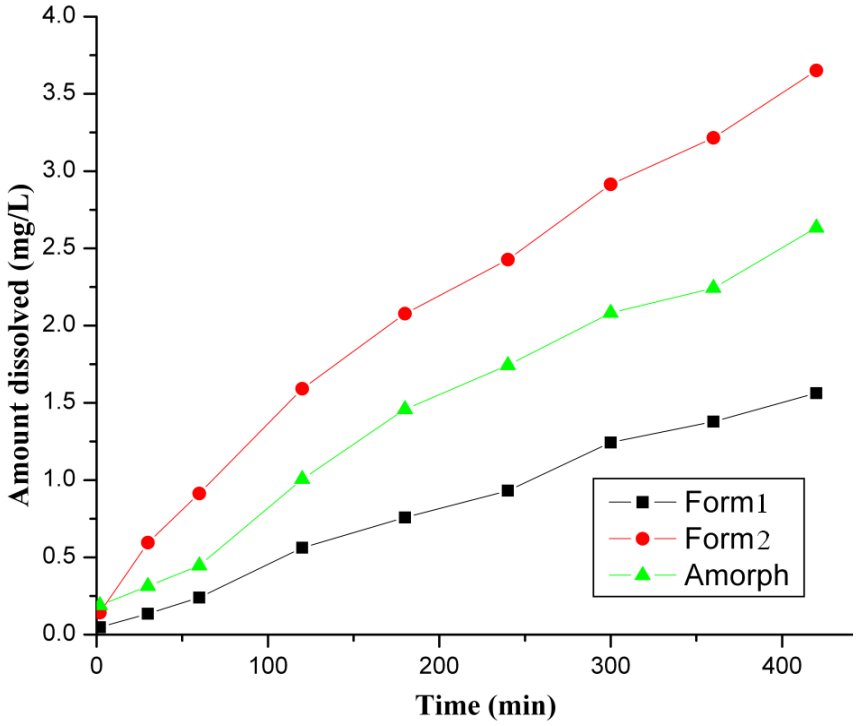

Fig. S11 Dissolution rate of Curcumin polymorphs in 40% EtOH-water at 37 °C.