Mechanical Anisotropy and Tabletability of Famotidine Polymorphs

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Supplementary Information

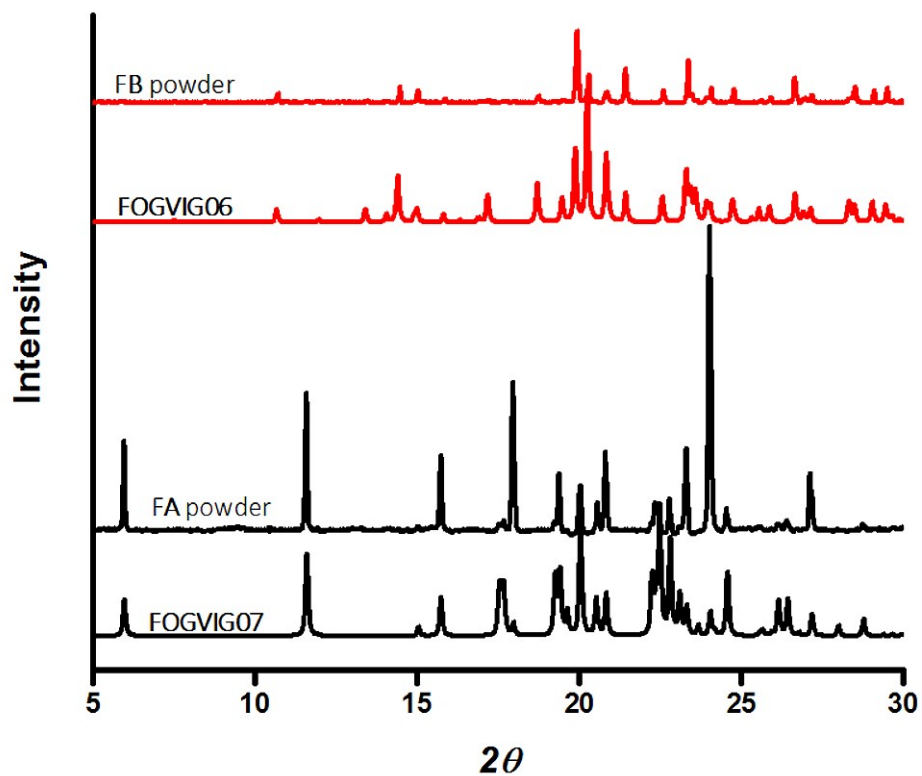**S1. Experimental and simulated PXRD patterns for famotidine bulk phases**

Figure S1. PXRD patterns for the bulk powders of FA and FB, compared to reference patterns obtained from FOGVIG06 and FOGVIG07 in the CSD.

S2. Face identification of single crystals

Major faces for indentation of both polymorphs were identified on a Bruker D8-QUEST diffractometer, using the *APEX3* software. SEM images were also collected for bulk samples to correlate the identified faces with the crystal morphology.
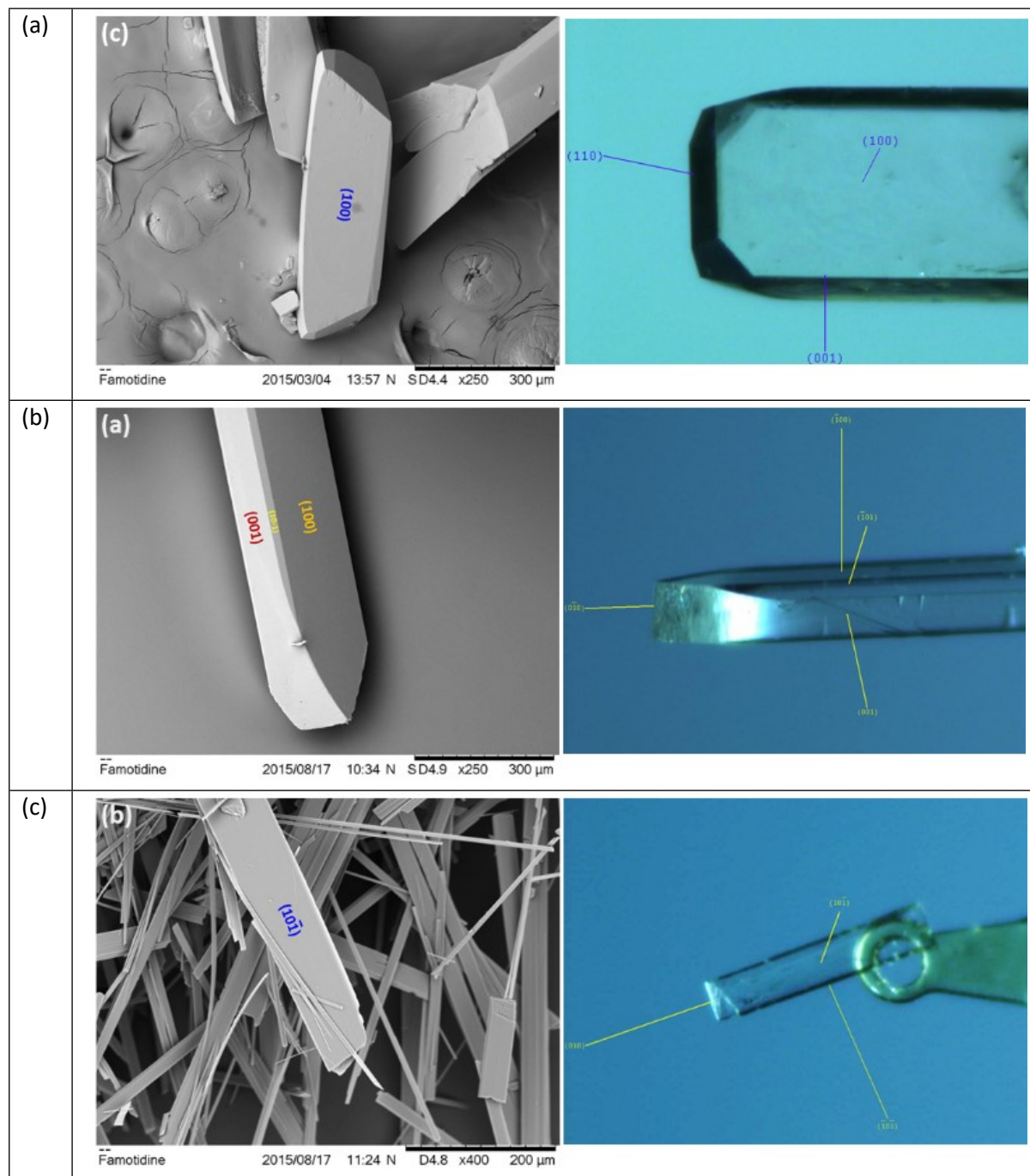

Figure S2. SEM images and face-indexed crystals of: (a) form A: {100} and {001} are the major faces; (b) form B, columnar-shaped crystals: {100} is the major face; (c) form B lath-shaped crystals: {10–1} is the major face. Form B indexing refers to the $P2_1/n$ setting (a, b ,c ≈ 17.0, 5.3, 17.8 Å, β ≈ 117°).

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S3. PIXEL calculations: Form A (CSD: FOGVIG07, space group $P2_1/c$)

<u>**Unit cell:**</u> a = 11.978, b = 7.196, c = 16.812 Å, alpha = 90, beta = 99.77, gamma = 90°

<u>**Symmetry operators:**</u>   [1]   x, y, z   [2]   −x, ½+y, ½−z   [3]   −x, −y, −z   [4]   x, ½−y, ½+z

Only interactions with magnitude > 3 kJ mol^{-1} are listed.

Mol 1 ARU	Mol 2 ARU	Mol 1 Operator	Mol 2 Operator	Distance	Coulomb	Polarisation	Dispersion	Repulsion	Total
1_555_01	3_756_01	x,y,z	2-x,-y,1-z	10.621	-74.4	-36.0	-49.7	71.6	-88.6
1_555_01	3_657_01	x,y,z	1-x,-y,2-z	12.969	-134.8	-66.3	-37.2	151.3	-86.9
1_555_01	4_554_01	x,y,z	x,0.5-y,-0.5+z	8.408	-34.5	-18.5	-46.0	35.4	-63.5
1_555_01	4_555_01	x,y,z	x,0.5-y,0.5+z	8.408	-34.5	-18.5	-46.0	35.4	-63.5
1_555_01	2_646_01	x,y,z	1-x,-0.5+y,1.5-z	7.219	-35.9	-19.8	-50.0	49.8	-55.8
1_555_01	2_656_01	x,y,z	1-x,0.5+y,1.5-z	7.219	-35.9	-19.8	-50.0	49.8	-55.8
1_555_01	1_545_01	x,y,z	x,-1+y,z	7.196	-42.1	-23.6	-29.9	52.6	-43.0
1_555_01	1_565_01	x,y,z	x,1+y,z	7.196	-42.1	-23.6	-29.9	52.6	-43.0
1_555_01	3_667_01	x,y,z	1-x,1-y,2-z	12.870	-25.2	-5.6	-17.5	15.0	-33.4
1_555_01	2_746_01	x,y,z	2-x,-0.5+y,1.5-z	7.126	-7.8	-6.8	-30.1	20.6	-24.1
1_555_01	2_756_01	x,y,z	2-x,0.5+y,1.5-z	7.126	-7.8	-6.8	-30.1	20.6	-24.1
1_555_01	3_766_01	x,y,z	2-x,1-y,1-z	10.501	-1.1	-1.3	-13.8	2.3	-14.0
1_555_01	4_544_01	x,y,z	x,-0.5-y,-0.5+z	11.181	1.0	-1.5	-4.2	0.4	-4.3
1_555_01	4_545_01	x,y,z	x,-0.5-y,0.5+z	11.181	1.0	-1.5	-4.2	0.4	-4.3
1_555_01	3_656_01	x,y,z	1-x,-y,1-z	8.942	-1.6	-0.8	-1.9	0.0	-4.2
1_555_01	4_565_01	x,y,z	x,1.5-y,0.5+z	10.951	-2.6	-0.2	-0.9	0.0	-3.7
1_555_01	4_564_01	x,y,z	x,1.5-y,-0.5+z	10.951	-2.6	-0.2	-0.9	0.0	-3.7

S3. PIXEL calculations: Form B (CSD: FOGVIG06, space group $P2_1/n$)

Unit cell: a = 17.048, b = 5.329, c = 17.762Å, alpha = 90, beta = 116.58, gamma = 90°

Symmetry operators: [1] x, y, z [2] ½–x, ½+y, ½–z [3] –x, –y, –z [4] ½+x, ½–y, ½+z

Only interactions with magnitude > 3 kJ mol^{-1} are listed.

Mol 1 ARU	Mol 2 ARU	Mol 1 Operator	Mol 2 Operator	Distance	Coulomb	Polarisation	Dispersion	Repulsion	Total
1_555_01	1_565_01	x,y,z	x,1+y,z	5.329	-66.0	-31.4	-78.9	78.2	-98.1
1_555_01	1_545_01	x,y,z	x,-1+y,z	5.329	-66.0	-31.4	-78.9	78.2	-98.1
1_555_01	3_666_01	x,y,z	1-x,1-y,1-z	9.054	-72.2	-19.8	-38.1	38.6	-91.5
1_555_01	2_545_01	x,y,z	0.5-x,-0.5+y,0.5-z	8.996	-72.6	-31.4	-32.6	61.7	-74.9
1_555_01	2_555_01	x,y,z	0.5-x,0.5+y,0.5-z	8.996	-72.6	-31.4	-32.6	61.7	-74.9
1_555_01	4_565_01	x,y,z	0.5+x,1.5-y,0.5+z	9.154	-82.1	-42.6	-34.7	94.8	-64.5
1_555_01	4_464_01	x,y,z	-0.5+x,1.5-y,-0.5+z	9.154	-82.1	-42.6	-34.7	94.8	-64.5
1_555_01	3_576_01	x,y,z	-x,2-y,1-z	8.823	-18.4	-10.3	-35.2	44.4	-19.5
1_555_01	2_556_01	x,y,z	0.5-x,0.5+y,1.5-z	9.556	-11.9	-5.5	-21.7	20.9	-18.1
1_555_01	2_546_01	x,y,z	0.5-x,-0.5+y,1.5-z	9.556	-11.9	-5.5	-21.7	20.9	-18.1
1_555_01	4_575_01	x,y,z	0.5+x,2.5-y,0.5+z	10.546	-6.3	-1.0	-5.1	1.9	-10.6
1_555_01	4_474_01	x,y,z	-0.5+x,2.5-y,-0.5+z	10.546	-6.3	-1.0	-5.1	1.9	-10.6
1_555_01	3_566_01	x,y,z	-x,1-y,1-z	8.878	-4.7	-1.6	-9.3	5.3	-10.3
1_555_01	2_565_01	x,y,z	0.5-x,1.5+y,0.5-z	11.736	-6.3	-0.4	-0.6	0.0	-7.2
1_555_01	2_535_01	x,y,z	0.5-x,-1.5+y,0.5-z	11.736	-6.3	-0.4	-0.6	0.0	-7.2
1_555_01	1_575_01	x,y,z	x,2+y,z	10.658	-3.6	-0.3	-0.6	0.0	-4.5
1_555_01	1_535_01	x,y,z	x,-2+y,z	10.658	-3.6	-0.3	-0.6	0.0	-4.5
1_555_01	3_656_01	x,y,z	1-x,-y,1-z	11.821	6.1	-0.9	-1.7	0.0	3.6
1_555_01	3_686_01	x,y,z	1-x,3-y,1-z	11.698	9.9	-0.5	-0.4	0.0	9.1
1_555_01	3_676_01	x,y,z	1-x,2-y,1-z	9.001	23.1	-5.0	-5.3	0.2	13.0

S4. Energy frameworks from *CrystalExplorer*

Energy frameworks were calculated for FA and FB using *CrystalExplorer* V.1764, based on Gaussian B3LYP-D2/6-31G(d,p) molecular wavefunctions. For each molecule in the asymmetric unit, the total calculated intermolecular interaction energy with another molecule is the sum of electrostatic, polarization, dispersion, and exchange-repulsion components with scaling factors of 1.057, 0.740, 0.871, and 0.618, respectively. The interaction energies of a selected molecule with all molecules having any atom within 3.8 Å were calculated. The interaction energies below 5 kJ mol^{-1} were omitted for clarity and the cylinder thickness was taken to be proportional to the intermolecular interaction energies in the energy framework. The resulting energy frameworks are comparable to the energy-vector diagrams calculated using *PIXEL*, and confirm the inherent 3-D (FA) and 2-D (RB) nature of the structures. The corrugated layers in FB parallel to $(10\bar{1})$ show a total intralayer energy of -242 kJ mol^{-1} but an interlayer energy of a -40 kJ mol^{-1}.

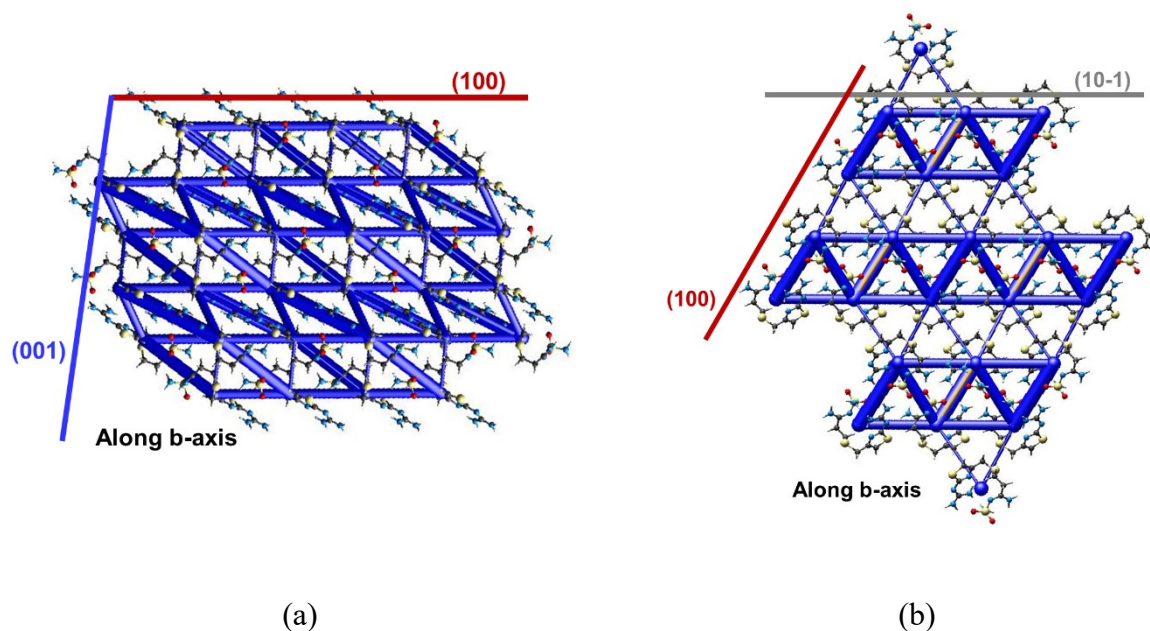(a)   (b)

Figure S3. *CrystalExplorer* energy frameworks for (a) FA and (b) FB viewed along the *b* axis. The thickness of each blue cylinder represents the relative strength of each pairwise intermolecular interaction. The minimum energy threshold is set at -5 kJ mol^{-1}. Red, blue, and gray bars represent the indentation planes (100), (001) and $(10\bar{1})$, respectively.