Supplementary information

Revealing the intergrowth phenomenon of aspirin polymorphs through a swift cooling crystallization process

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Theory:

Analytical classical nucleation theory approach

The interfacial or surface-free energy (γ) between the newly formed solid nuclei and mother liquor, is expressed as

$$\Delta Gs = 4\pi r^2\gamma \quad \textbf{(1)}$$

In accordance with the classical nucleation theory, the measured induction time and supersaturation value are used to calculate the homogenous formation of the spherical nuclei and their interfacial energy. The value of the interfacial free energy is estimated by the following relation,

$$ln\tau \infty [B/(lns)^2] \textbf{ where } B = [16\pi\gamma^3V^2/3k^3T^3] \quad \textbf{(2)}$$

B value is estimated from the slope, draw $1/(lns)^2 against\ ln\tau$

The change in the volume energy free energy (ΔG_V) can be denoted by

$$\Delta G_V = (4/3)\pi r^3(\Delta\mu/V) \quad \textbf{(3)}$$

$Here, \Delta\mu$ is the chemical potential between the newly formed crystalline phase and the mother liquor. We know $\Delta\mu$= -KTlnS. The free energy change of the transformation per unit volume of the solid phase (ΔGv), is associated with solute concentration.

$$\Delta Gv = -\frac{\left[(KTln\left(\frac{c}{c^*}\right))\right]}{V}(or) \ -[(KT(1+s))/V] \quad \textbf{(4)}$$

Where, ΔGv-Change in the volume free energy per unit volume of the solid, K-Boltzmann constant (3.81×10^{-21} m^2 kg s^{-2} k=R/N), R-Gas constant (8.3145 $Jmol^{-1}$ K^{-1}), N- Avogadro number ($6.023 \times 10^{23}\ mol^{-1}$), T-Temperature of the solution in Kelvin, V-Molar volume of the crystal, C and C*-Actual and equilibrium concentration of aspirin solute, S-Supersaturation ratio (S= C/C*). When C<C*, nucleation does not happen because S is

zero or lower in value, so volume-free energy is also zero. On the other hand, when C>C*, nucleation occurs spontaneously because supersaturation is positive and volume-free energy is negative. By rearranging equations 4 and 5 to get

$$\Delta G_V = (4/3)\pi r^3 \Delta G_v \quad \textbf{(5)}$$

The overall free energy barrier for the formed ASP nuclei is a sum of the surface and volume free energy of the newly formed nuclei.

$$\Delta G = \Delta G_S + \Delta G_V \quad \textbf{(6)}$$

$$\Delta G = 4\pi r^2 \gamma + (4/3)\pi r^3 \Delta G_v \quad \textbf{(7)}$$

The critical size of a stable spherical nucleus is r*. When the radius of a nucleus is less than r*, it will dissolve or disintegrate into the solution; when the radius is more than r*, the nucleus stays stable and grows continuously. When r = r* is the critical size, dΔG/dr = 0, it is defined as follows

$$r^* = -\left(\frac{2\gamma}{\Delta G v}\right) \quad \textbf{(8)}$$

The critical energy barrier for nucleation ΔG^* were calculated using the following relations

$$\Delta G^* = 16\pi\gamma^3 v^2/3(\Delta G v)^2 \quad \textbf{(9)}$$

The number of molecules in the critical nuclei (i*) was calculated by

$$i^* = \left[4\pi(r^*)^3\right]/3V \quad \textbf{(10)}$$

The nucleation rate J is defined as the number of critical nuclei formed per unit time per unit volume, as expressed in the form of the Arrhenius reaction velocity relation,

$$J = A\, exp(-\frac{\Delta G^*}{KT}) \quad \textbf{(11)}$$

$$J = A\, exp[-(16\pi\gamma^3 V^2)/(3k^3T^3(lnS)^2)] \quad \textbf{(12)}$$

Where A is the pre-exponential factor (10^{25}).

Table S1. Nucleation parameters of stable Form-I polymorph of aspirin.

σ	$r^*_{S(F-I)}$ ($\times 10^{-9}$m)	$i^*_{S(F-I)}$	$\gamma_{S(F-I)}$ (mJm^{-2})	$\Delta G^*_{S(F-I)}$ ($\times 10^{-20}$Jmol^{-1})	$\Delta Gv_{S(F-I)}$ ($\times 10^{7}$Jm^{-3})	$J_{S(F-I)}$ ($\times 10^{22}$m^{-3}s^{-1})
0.20	1.38E-09	50.9219	2.9387	2.33E-20	-4271761	4.79E+22
0.24	1.31E-09	43.8259	3.2030	2.30E-20	-4894777	5.07E+22
0.27	1.25E-09	38.2876	3.4537	2.26E-20	-5520972	5.39E+22
0.30	1.2E-09	34.0520	3.6999	2.24E-20	-6150321	5.56E+22
0.33	1.16E-09	30.5839	3.9369	2.22E-20	-6782787	5.75E+22
0.37	1.12E-09	27.6910	4.1655	2.20E-20	-7418321	5.95E+22
0.40	1.09E-09	25.2404	4.3864	2.18E-20	-8056859	6.16E+22
0.43	1.06E-09	23.1372	4.6003	2.16E-20	-8698322	6.39E+22
0.47	1.03E-09	21.3116	4.8075	2.13E-20	-9342613	6.63E+22
0.50	1E-09	19.7112	5.0084	2.11E-20	-9989615	6.9E+22
0.53	9.78E-10	18.2962	5.2033	2.09E-20	-1.1E+07	7.18E+22
0.57	9.55E-10	17.0353	5.3923	2.06E-20	-1.1E+07	7.5E+22
0.60	9.34E-10	15.9038	5.5755	2.04E-20	-1.2E+07	7.84E+22
0.64	9.13E-10	14.8820	5.7530	2.01E-20	-1.3E+07	8.21E+22
0.68	8.94E-10	13.9537	5.9248	1.98E-20	-1.3E+07	8.62E+22
0.71	8.75E-10	13.1057	6.0908	1.95E-20	-1.4E+07	9.07E+22

Table S2. Nucleation parameters of metastable Form-II polymorph of aspirin.

σ	$r^*_{MS(F-II)}$ ($\times 10^{-10}$m)	$i^*_{MS(F-II)}$	$\gamma_{MS(F-II)}$ (mJm^{-2})	$\Delta G^*_{MS(F-II)}$ ($\times 10^{-20}$Jmol^{-1})	$\Delta Gv_{MS(F-II)}$ ($\times 10^{7}$Jm^{-3})	$J_{MS(F-II)}$ ($\times 10^{23}$m^{-3}s^{-1})
1.28	6.24E-10	4.7460	7.3625	1.20E-20	-2.4E+07	4.79E+23
1.31	6.14E-10	4.5273	7.4290	1.17E-20	-2.4E+07	5.07E+23
1.35	6.04E-10	4.3169	7.4861	1.15E-20	-2.5E+07	5.38E+23
1.38	5.95E-10	4.1139	7.5332	1.12E-20	-2.5E+07	5.74E+23
1.42	5.85E-10	3.9168	7.5690	1.09E-20	-2.6E+07	6.15E+23
1.45	5.81E-10	3.8261	7.6610	1.08E-20	-2.6E+07	6.15E+23
1.49	5.71E-10	3.6426	7.6783	1.05E-20	-2.7E+07	6.63E+23

Table S3. Nucleation parameters of an unstable polymorph of aspirin.

σ	r^*_{US} ($\times 10^{-10}$m)	i^*_{US}	γ_{US} (mJm^{-2})	ΔG^*_{US} ($\times 10^{-20}$Jmol^{-1})	ΔGv ($\times 10^{7}$Jm^{-3})	$J_{US(F-I)}$ ($\times 10^{24}$m^{-3}s^{-1})
1.52	5.2E-10	2.7538	7.1172	8.07E-21	-2.7E+07	1.23E+24
1.55	5.04E-10	2.5017	7.0045	7.45E-21	-2.8E+07	1.44E+24
1.58	5.01E-10	2.4563	6.9500	7.20E-21	-2.8E+07	1.44E+24
1.6	4.98E-10	2.4150	6.9019	6.70E-21	-2.9E+07	1.44E+24
1.63	4.28E-10	1.5289	6.2186	4.74E-21	-2.9E+07	2.87E+24
1.65	4.26E-10	1.5074	6.1925	4.72E-21	-2.9E+07	2.87E+24

Table S4. Lattice parameters of the grown aspirin polymorphs compared with literature values.

Lattice Parameters	Form-I		Form-II	
	Present work	Literature Value	Present work	Literature value
a (Å)	11.398	11.277	12.084	12.151
b (Å)	6.550	6.551	6.477	6.506
c (Å)	11.539	11.274	11.431	11.367
β (°)	95.21	95.83	111.91	111.57
Volume (Å^3)	825.87	828.71	830.16	835.79