SUPPLEMENTARY INFORMATION

Precision measurement of the growth rate and mechanism of ibuprofen {001} and {011} as a function of crystallization environment

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Abstract

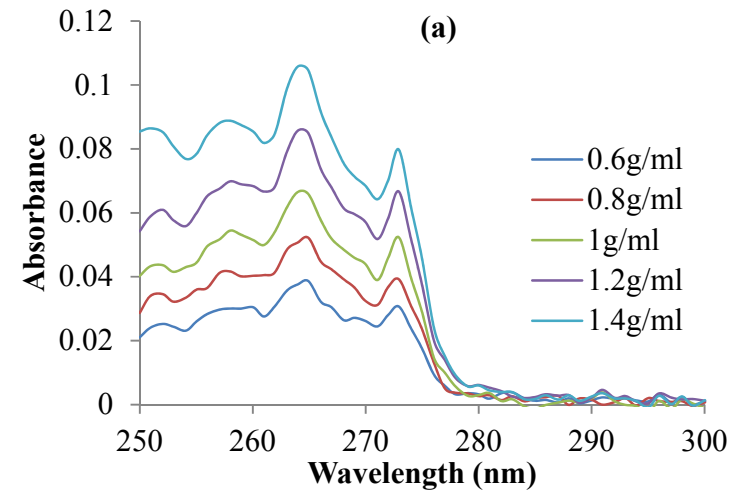
The crystallisation of ibuprofen under diffusion-limited conditions measured as a function of supersaturation, solvent and reactor scale is described in the main paper and in this supplementary material some additional information is provided. This comprises:

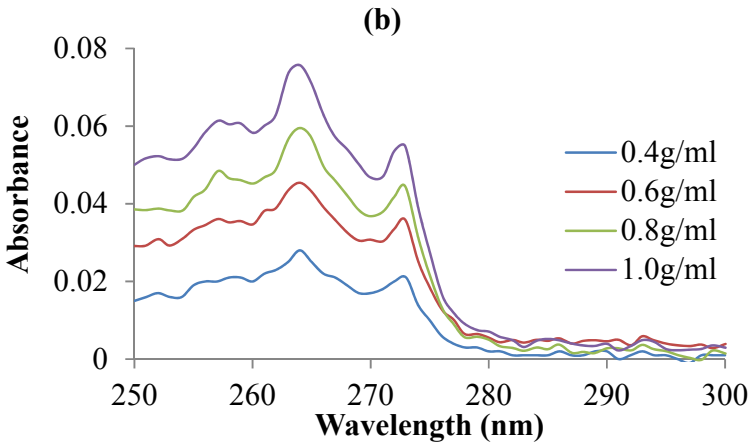
- Details concerning the raw ATR UV/Vis spectra collected and the associated calibration used to determine the concentration of ibuprofen in 95% ethanol/water, ethyl acetate, and acetonitrile solvents as a function of temperature (section S1.1)
- Details of the gravimetric calculations used for the determination of the solubility of ibuprofen in toluene solutions (section S1.2)
- All the raw in-situ microscopy image data and its associated analysis which underpin the determination of face-specific growth rates as presented in the main paper (section S2).

S1. Data related to solubility determination in 95% ethanol/water, ethyl acetate, and acetonitrile solvents by ATR UV/Vis spectroscopy

S1. 1 ATR UV/Vis method development

The Beer-Lambert law states that the absorbance of a solution is directly proportional to the concentration of the absorbing species in the solution and the path length. Hence, ATR UV/Vis spectroscopy can be employed to determine the concentration of ibuprofen in a solution for a fixed path length. The calibration curve of ibuprofen was determined by measuring absorbance versus a range of concentrations using the specific absorbance peak of ibuprofen at 264 nm (Figure S1).





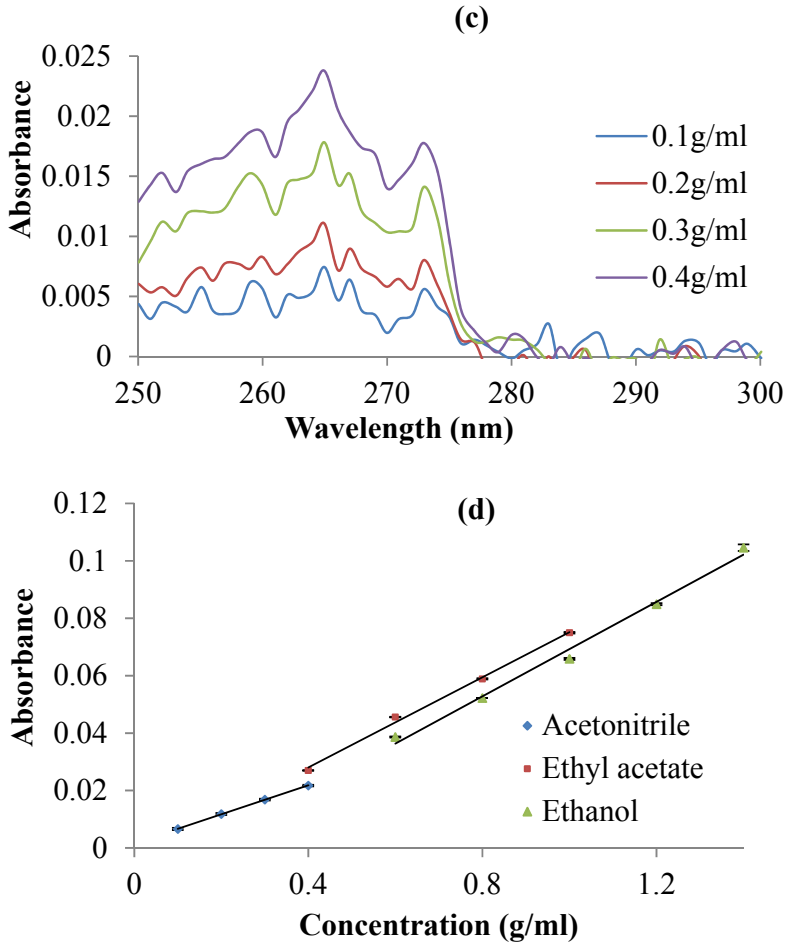


Figure S1 Spectra of ibuprofen in 95% ethanol/water (a), ethyl acetate (b) and acetonitrile (c) showing absorbance increase with increasing concentration of solutions and from these absorbances at 264 nm and known concentrations, calibration curves (d) were obtained.

Table S1 Calibration line of ibuprofen in 95% ethanol/water, ethyl acetate and acetonitrile at temperature from 15-35^{o}C

Solvents	Calibration line
95% Ethanol/Water	y = 0.0818x – 0.0172
Ethyl acetate	y = 0.0786x – 0.0034
Acetonitrile	y = 0.0503x + 0.0017

Table S1 shows the regression fits obtained from the calibration curves from which the solubility of ibuprofen in these 3 solvents over the temperature range 15-35^{o}C was determined.

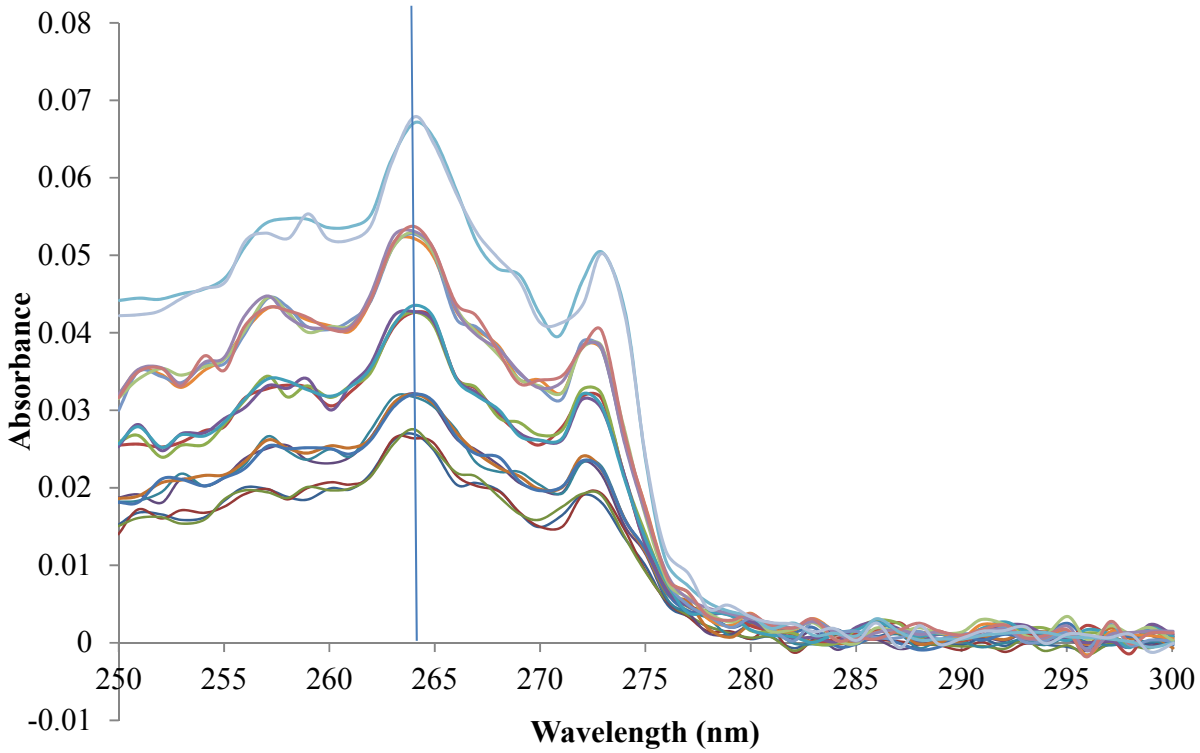


Figure S2 An example of spectra of ibuprofen in ethyl acetate at 15, 20, 25, 30 and 35°C showing absorbances increase with increasing temperature of saturated solutions and λmax does not shift with temperature

Spectroscopic exanimation of the ibuprofen solutions in the UV region revealed a strong absorbance maximum at about 264 nm. The λmax was not found to shift even in different solvents and concentration nor even as a function of temperature.

The ATR-UV/Vis spectroscopy calibration shows a linear correlation between UV/Vis absorbance intensity and the solute concentration for different concentrations of ibuprofen in

solvents. For a constant solution concentration, absorbance was found to be quite constant as a function of a temperature, as shown in Figure S2.

S1.2 Data related to solubility determination toluene solvents by gravimetric methods

Table S2 provides the raw gravimetric data together with the associated determination of the solubility of ibuprofen in toluene solutions over the temperature range from 15-35°C was determined.

Table S2 Solubility of ibuprofen in toluene solutions over the temperature range from 15-35°C

T(°C)	15	20	25	30	35
Sample 1	0.367	0.46	0.588	0.75	0.913
Sample 2	0.366	0.46	0.591	0.753	0.974
Sample 3			0.588		0.936
C(g/g)	0.367	0.46	0.589	0.7515	0.941
STDEV			0.00173	0.00212	0.03080

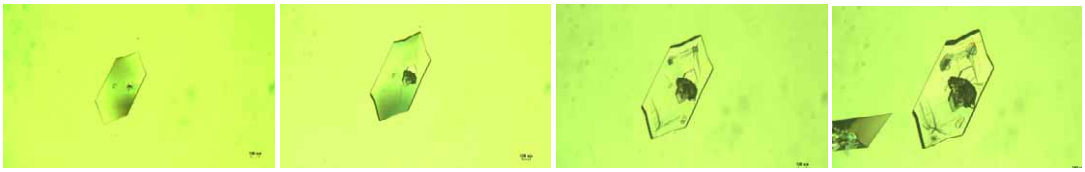
S2. Crystal growth rate measurement in the 0.5ml cuvette cell and the 15ml jacketed vessel

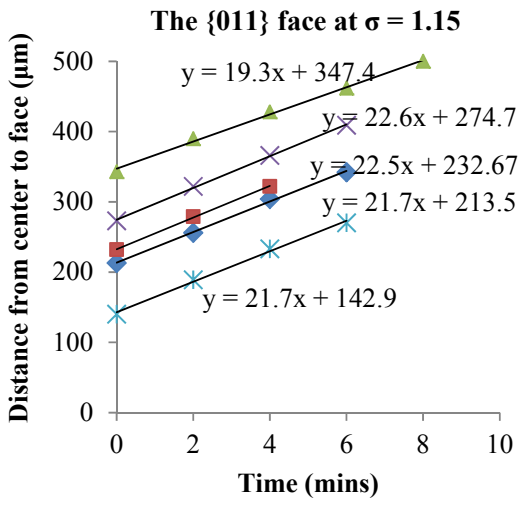
The data presented comprises plots of growth rate versus time for the {011} and {001} faces for all the crystals measured together with a representative image set for one of these crystals.

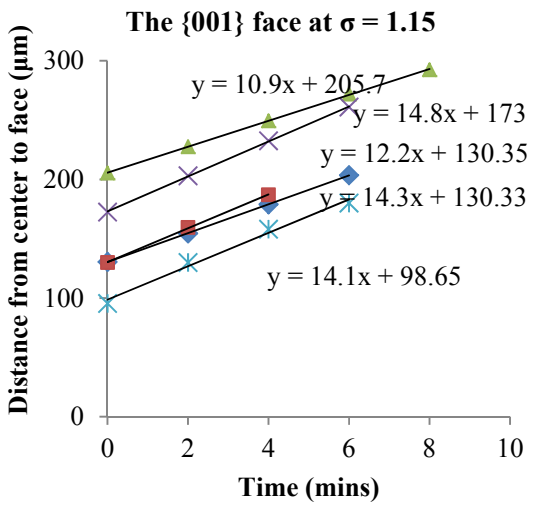
S2.1 Data from the 0.5ml cuvette cell

S2.1.1 95% Ethanol/Water Solutions

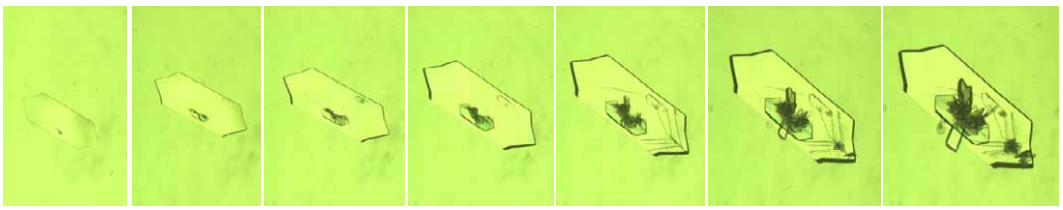
σ = 1.15

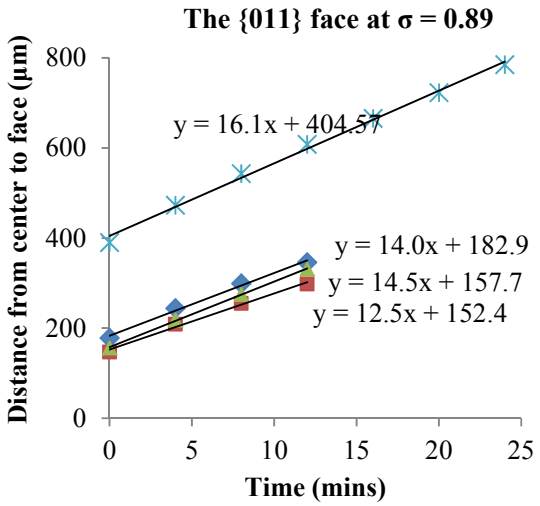


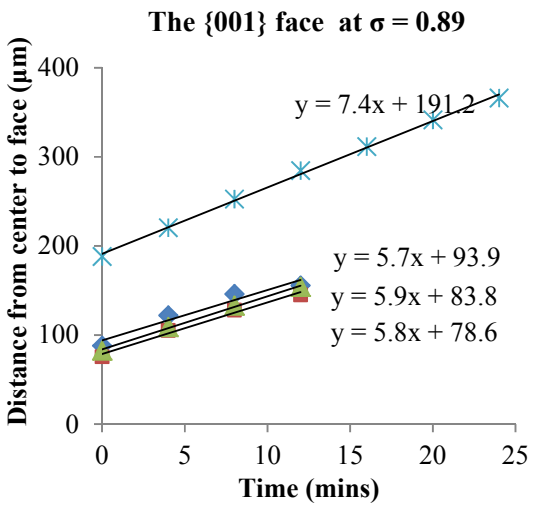




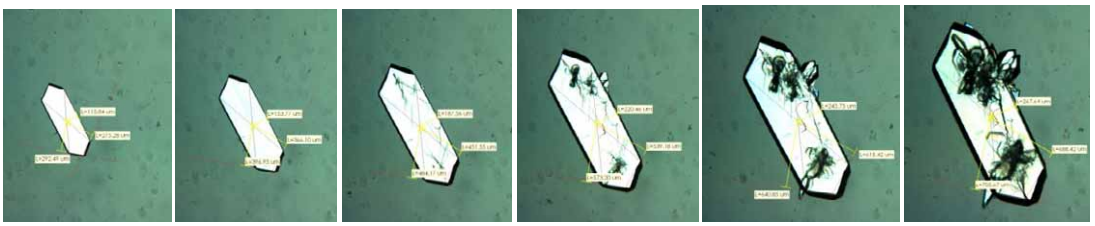
σ = 0.89

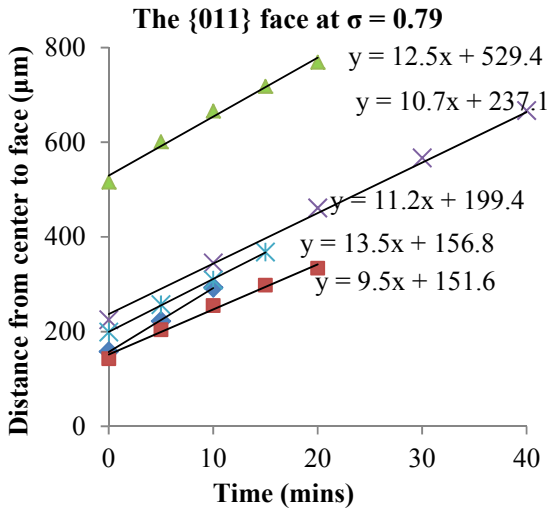


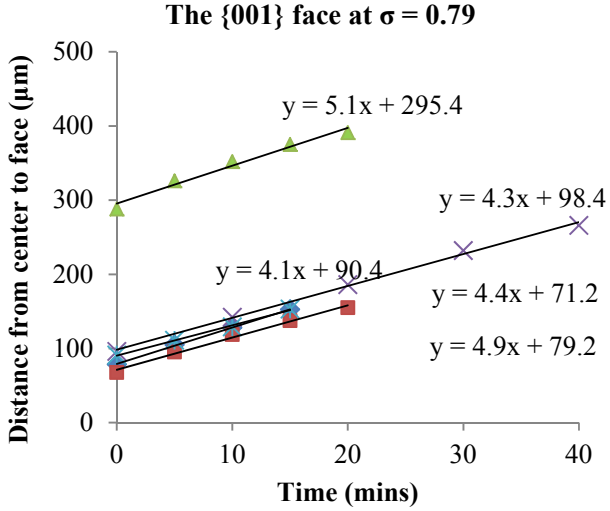

The {011} face at σ = 0.89
Distance from center to face (µm)
Time (mins)
y = 16.1x + 404.57
y = 14.0x + 182.9
y = 14.5x + 157.7
y = 12.5x + 152.4
0
200
400
600
800
0
5
10
15
20
25


The {001} face at σ = 0.89
Distance from center to face (µm)
Time (mins)
y = 7.4x + 191.2
y = 5.7x + 93.9
y = 5.9x + 83.8
y = 5.8x + 78.6
0
100
200
300
400
0
5
10
15
20
25

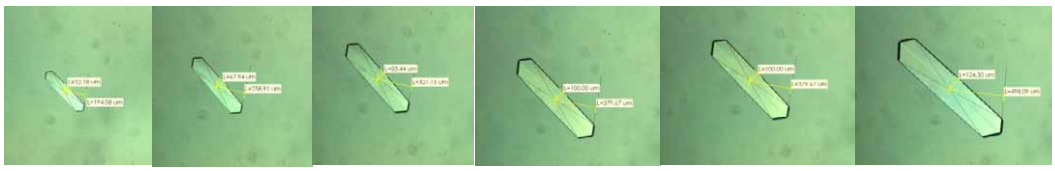
σ = 0.79

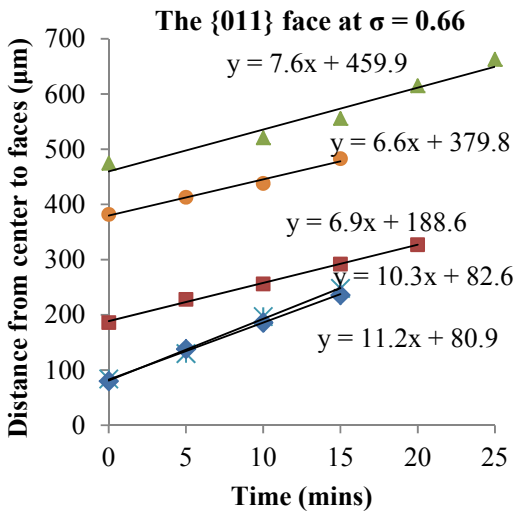


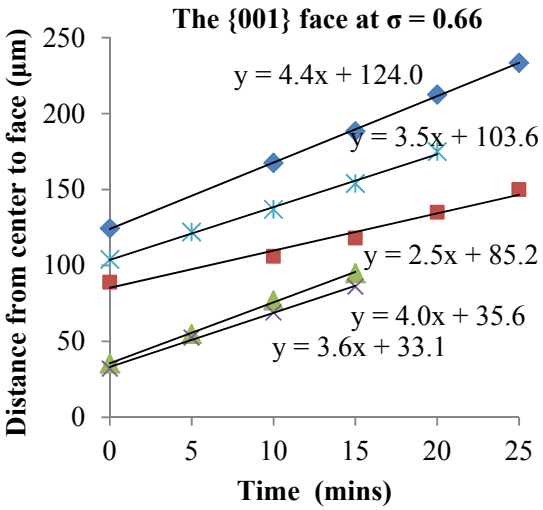

The {011} face at σ = 0.79
Distance from center to face (µm)
Time (mins)
y = 12.5x + 529.4
y = 10.7x + 237.1
y = 11.2x + 199.4
y = 13.5x + 156.8
y = 9.5x + 151.6
0
200
400
600
800
0
10
20
30
40


The {001} face at σ = 0.79
Distance from center to face (µm)
Time (mins)
y = 5.1x + 295.4
y = 4.3x + 98.4
y = 4.1x + 90.4
y = 4.4x + 71.2
y = 4.9x + 79.2
0
100
200
300
400
500
0
10
20
30
40

σ = 0.66

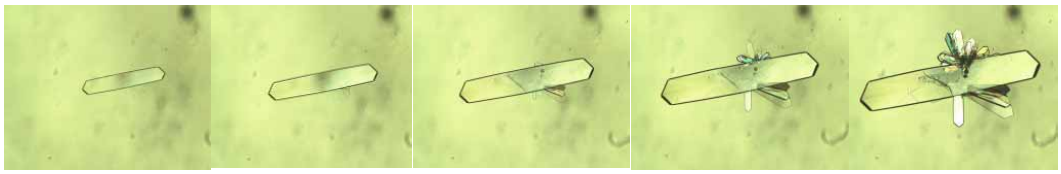


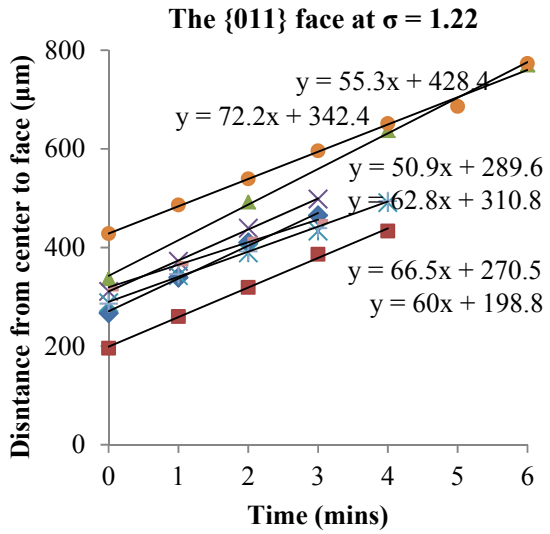


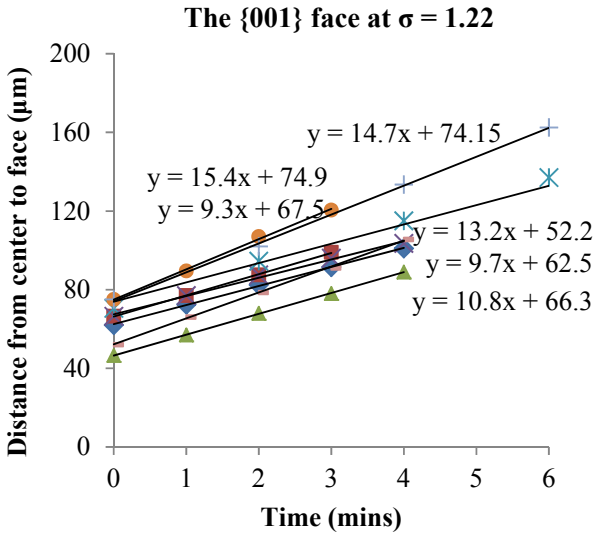


S2.1.2 Ethyl Acetate Solutions

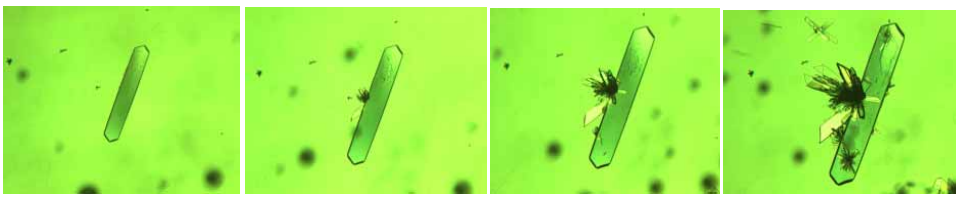
σ = 1.12

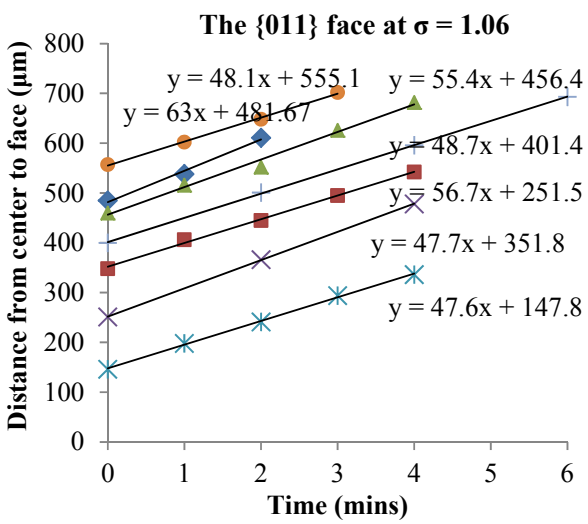


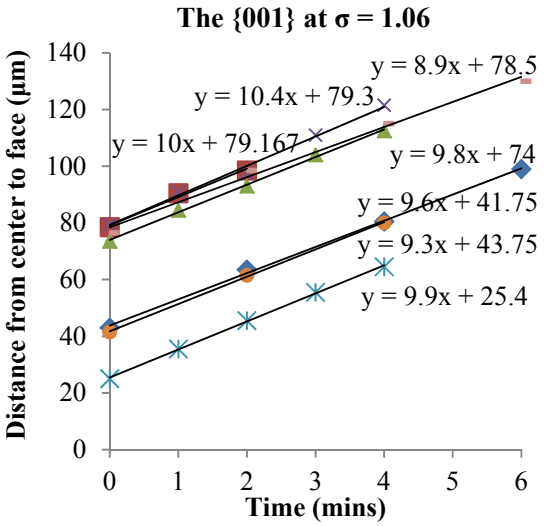




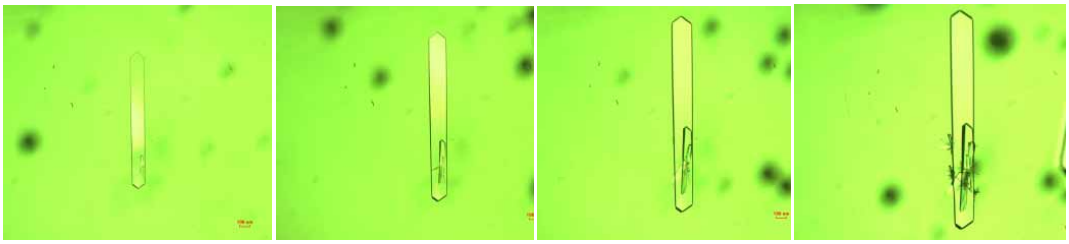
σ = 1.06

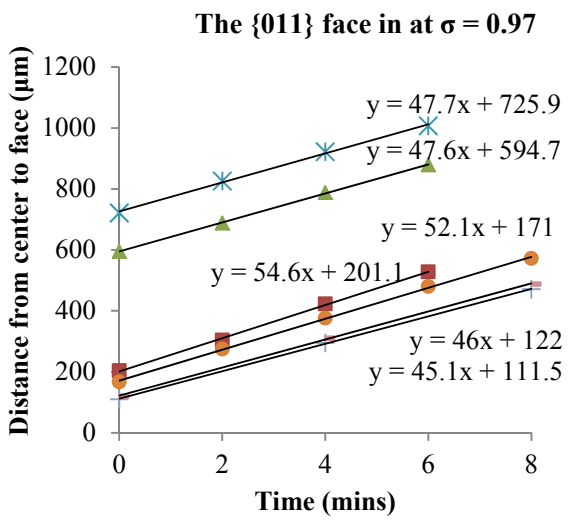


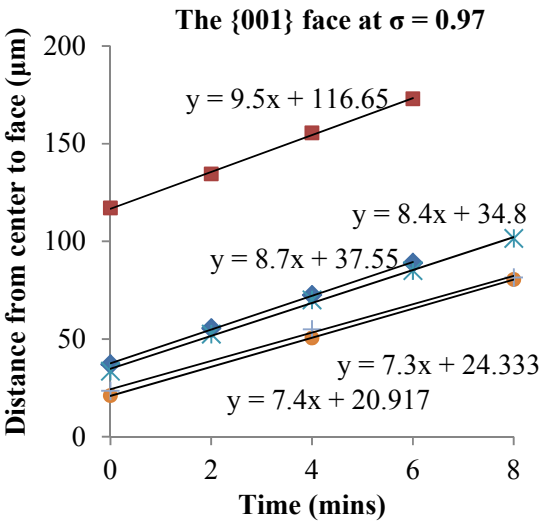

The {011} face at σ = 1.06
Distance from center to face (µm)
Time (mins)
y = 48.1x + 555.1
y = 55.4x + 456.4
y = 63x + 481.67
y = 48.7x + 401.4
y = 56.7x + 251.5
y = 47.7x + 351.8
y = 47.6x + 147.8


The {001} at σ = 1.06
Distance from center to face (µm)
Time (mins)
y = 8.9x + 78.5
y = 10.4x + 79.3
y = 10x + 79.167
y = 9.8x + 74
y = 9.6x + 41.75
y = 9.3x + 43.75
y = 9.9x + 25.4

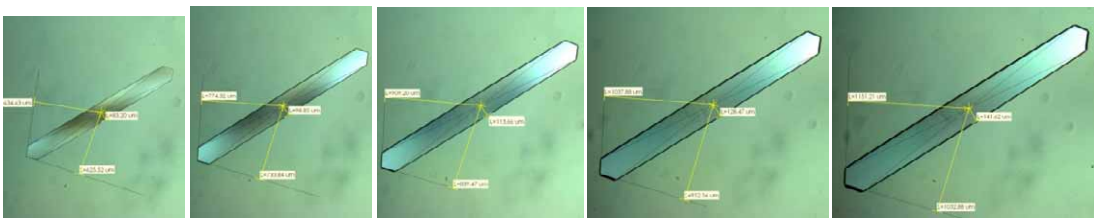
σ = 0.97

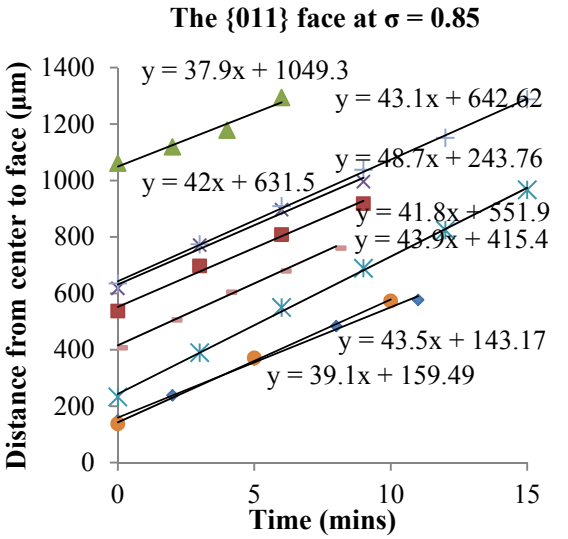


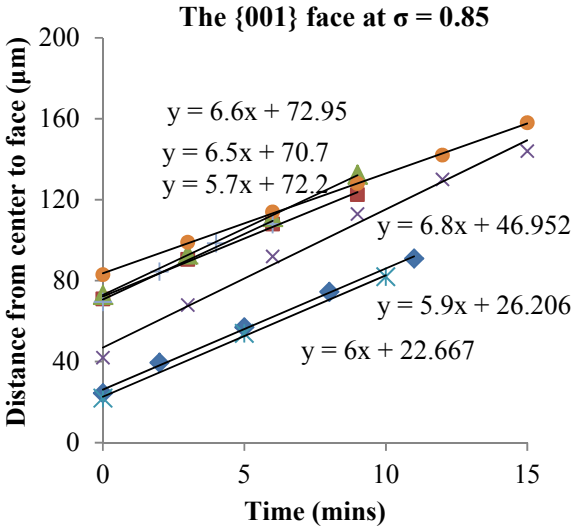

The {011} face in at σ = 0.97
Distance from center to face (µm)
Time (mins)
y = 47.7x + 725.9
y = 47.6x + 594.7
y = 52.1x + 171
y = 54.6x + 201.1
y = 46x + 122
y = 45.1x + 111.5


The {001} face at σ = 0.97
Distance from center to face (µm)
Time (mins)
y = 9.5x + 116.65
y = 8.4x + 34.8
y = 8.7x + 37.55
y = 7.3x + 24.333
y = 7.4x + 20.917

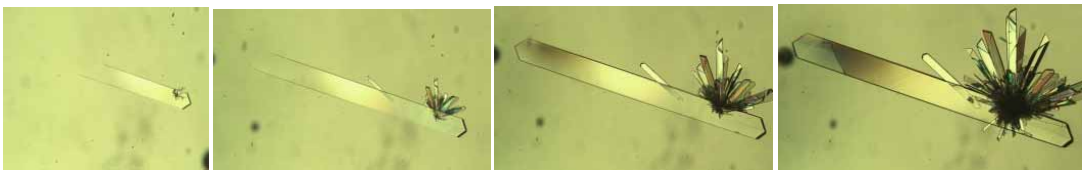
σ = 0.85

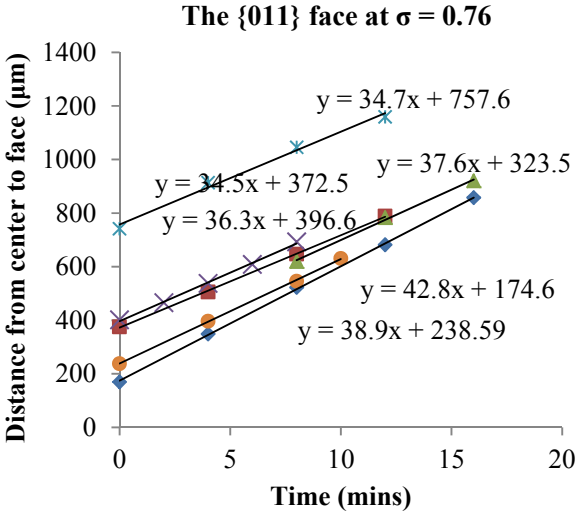


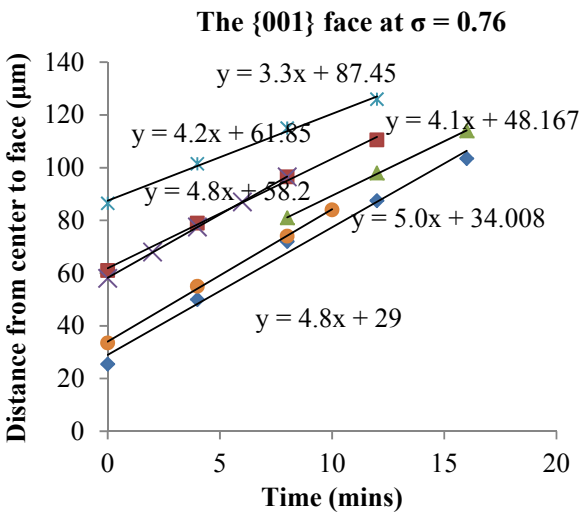

The {011} face at σ = 0.85
Distance from center to face (µm)
Time (mins)
y = 37.9x + 1049.3
y = 43.1x + 642.62
y = 48.7x + 243.76
y = 42x + 631.5
y = 41.8x + 551.9
y = 43.9x + 415.4
y = 43.5x + 143.17
y = 39.1x + 159.49


The {001} face at σ = 0.85
Distance from center to face (µm)
Time (mins)
y = 6.6x + 72.95
y = 6.5x + 70.7
y = 5.7x + 72.2
y = 6.8x + 46.952
y = 5.9x + 26.206
y = 6x + 22.667

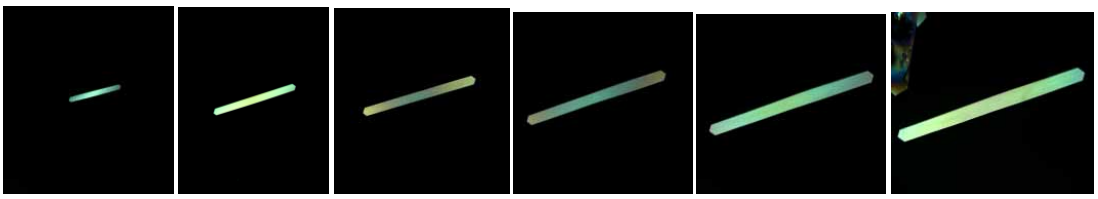
σ = 0.76

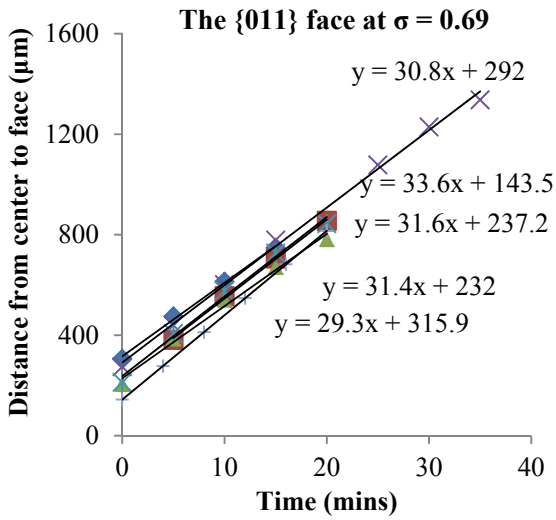


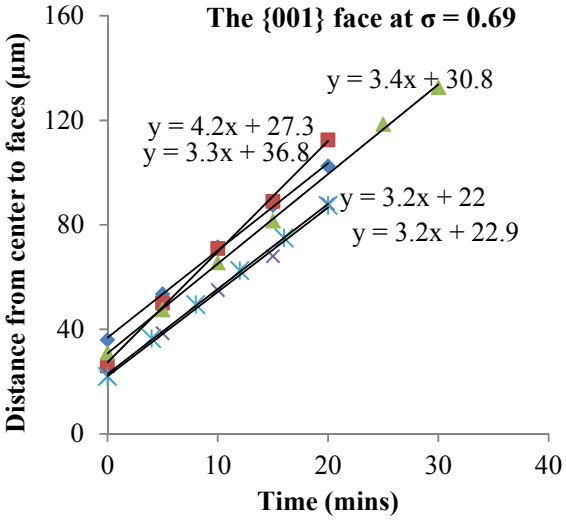

The {011} face at σ = 0.76
Distance from center to face (µm)
Time (mins)
y = 34.7x + 757.6
y = 37.6x + 323.5
y = 34.5x + 372.5
y = 36.3x + 396.6
y = 42.8x + 174.6
y = 38.9x + 238.59


The {001} face at σ = 0.76
Distance from center to face (µm)
Time (mins)
y = 3.3x + 87.45
y = 4.2x + 61.85
y = 4.1x + 48.167
y = 4.8x + 38.2
y = 5.0x + 34.008
y = 4.8x + 29

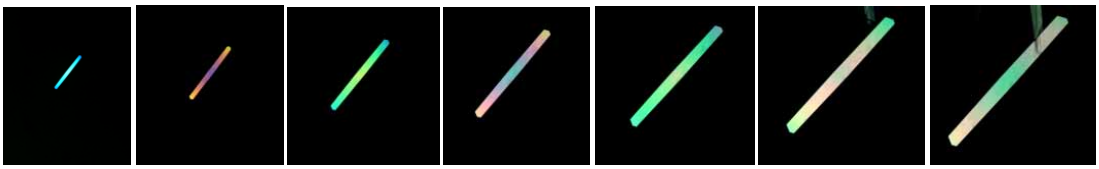
σ = 0.69

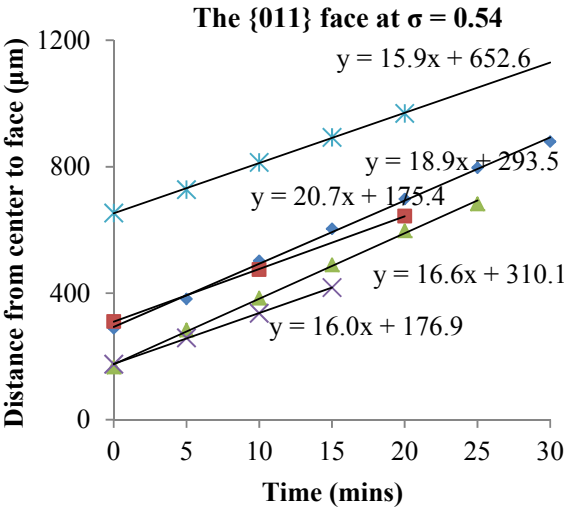


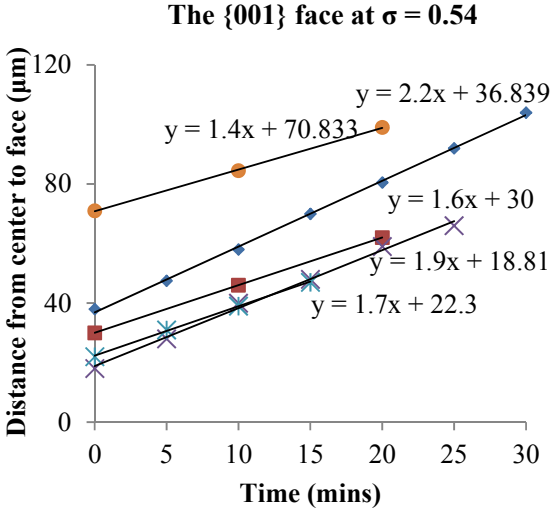

The {011} face at σ = 0.69
Distance from center to face (µm)
Time (mins)
y = 30.8x + 292
y = 33.6x + 143.5
y = 31.6x + 237.2
y = 31.4x + 232
y = 29.3x + 315.9
0
400
800
1200
1600
0
10
20
30
40


The {001} face at σ = 0.69
Distance from center to faces (µm)
Time (mins)
y = 3.4x + 30.8
y = 4.2x + 27.3
y = 3.3x + 36.8
y = 3.2x + 22
y = 3.2x + 22.9
0
40
80
120
160
0
10
20
30
40

σ = 0.54

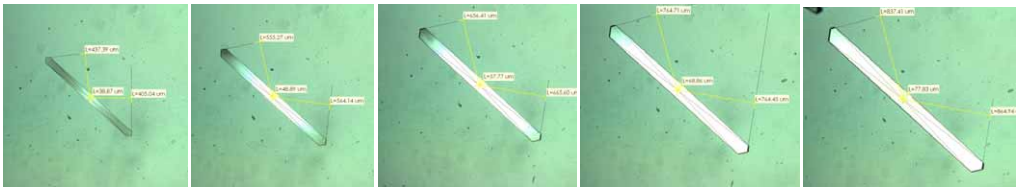


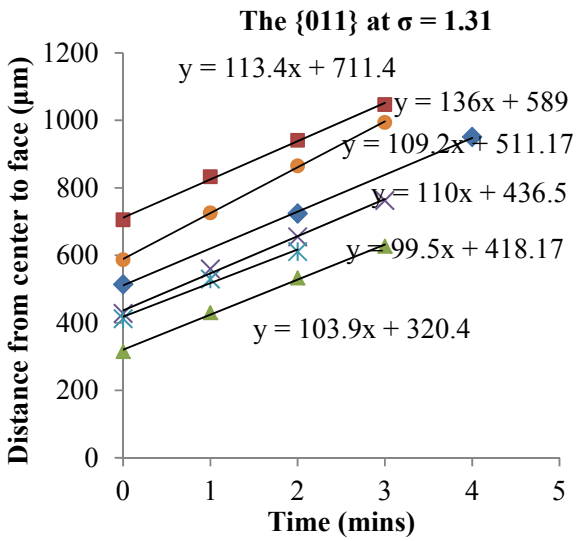

The {011} face at σ = 0.54
Distance from center to face (µm)
Time (mins)
y = 15.9x + 652.6
y = 18.9x + 293.5
y = 20.7x + 175.4
y = 16.6x + 310.1
y = 16.0x + 176.9
0
400
800
1200
0
5
10
15
20
25
30

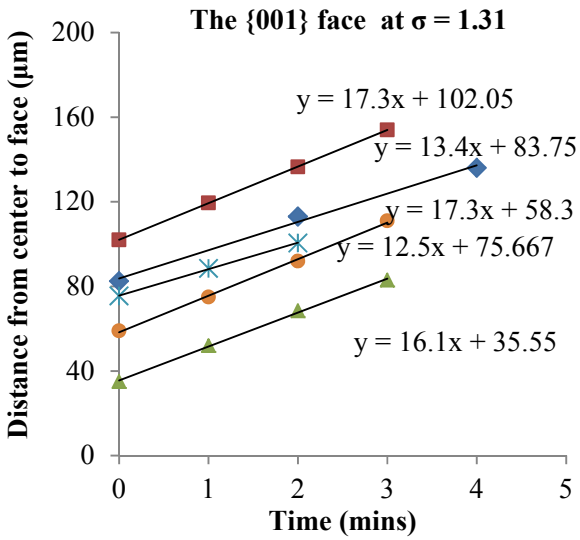

The {001} face at σ = 0.54
Distance from center to face (µm)
Time (mins)
y = 2.2x + 36.839
y = 1.4x + 70.833
y = 1.6x + 30
y = 1.9x + 18.81
y = 1.7x + 22.3
0
40
80
120
0
5
10
15
20
25
30

S2.1.3 Acetonitrile Solutions

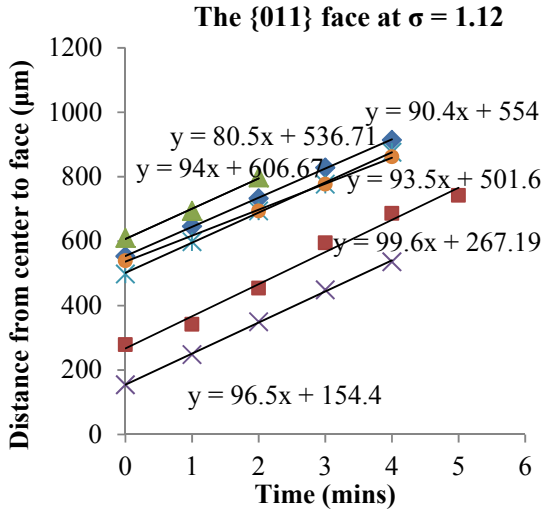
σ = 1.31

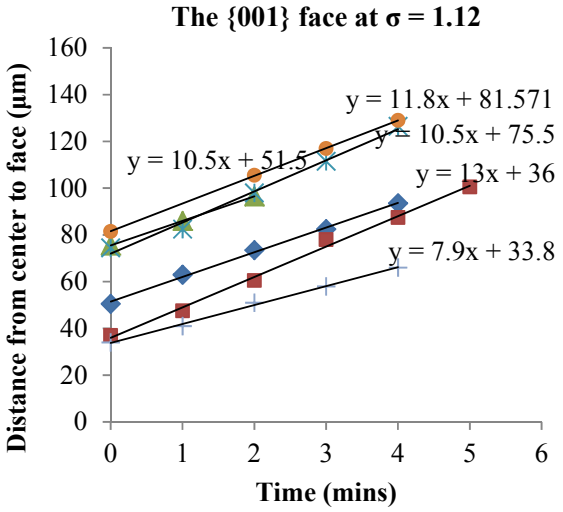




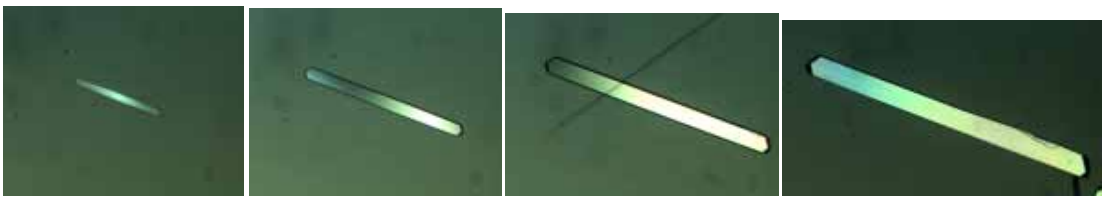


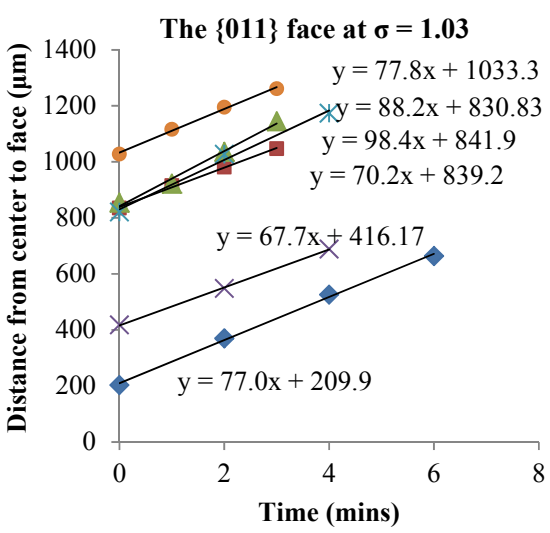
σ = 1.12

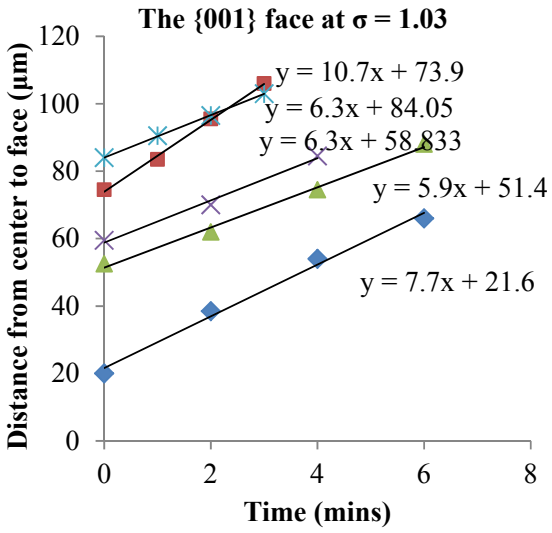




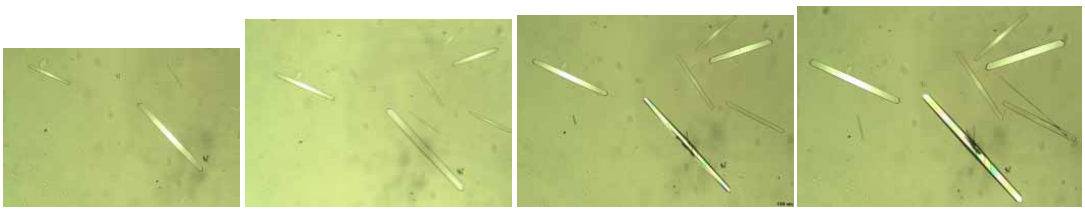
σ = 1.03

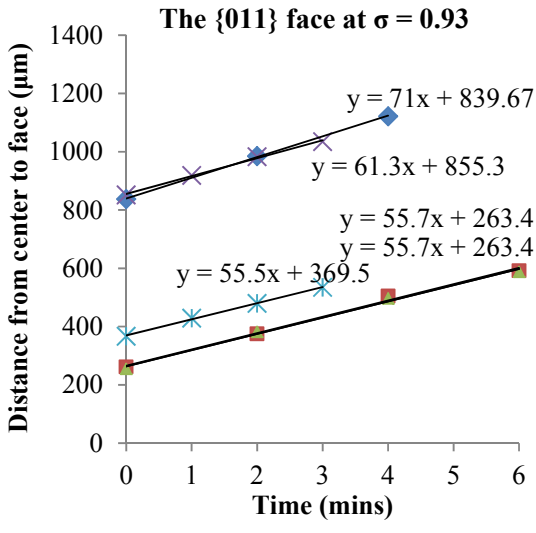


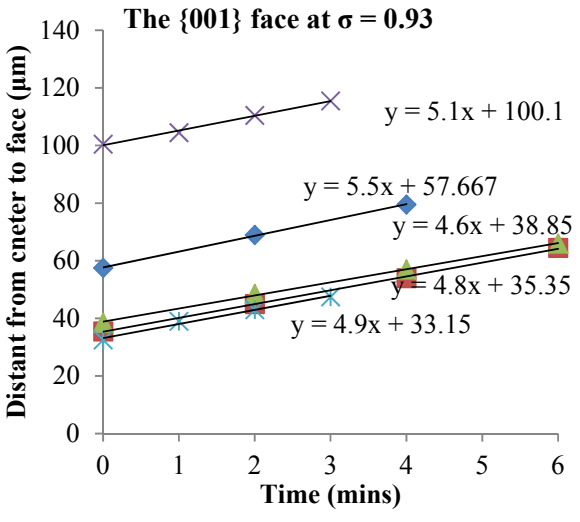

The {011} face at σ = 1.03
Distance from center to face (µm)
Time (mins)
y = 77.8x + 1033.3
y = 88.2x + 830.83
y = 98.4x + 841.9
y = 70.2x + 839.2
y = 67.7x + 416.17
y = 77.0x + 209.9


The {001} face at σ = 1.03
Distance from center to face (µm)
Time (mins)
y = 10.7x + 73.9
y = 6.3x + 84.05
y = 6.3x + 58.833
y = 5.9x + 51.4
y = 7.7x + 21.6

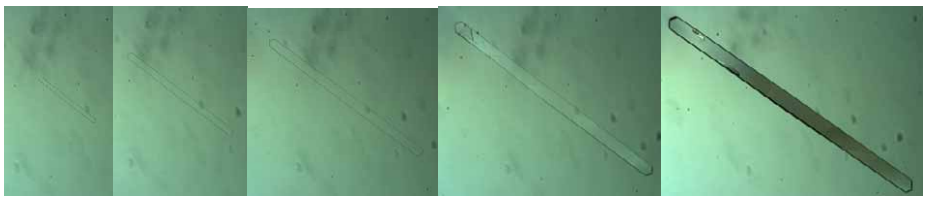
σ = 0.93

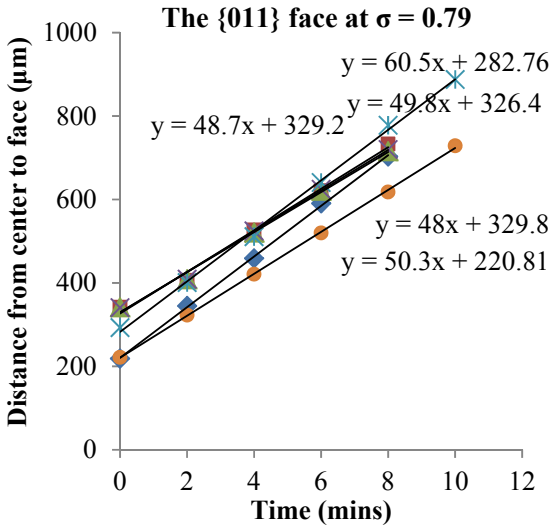


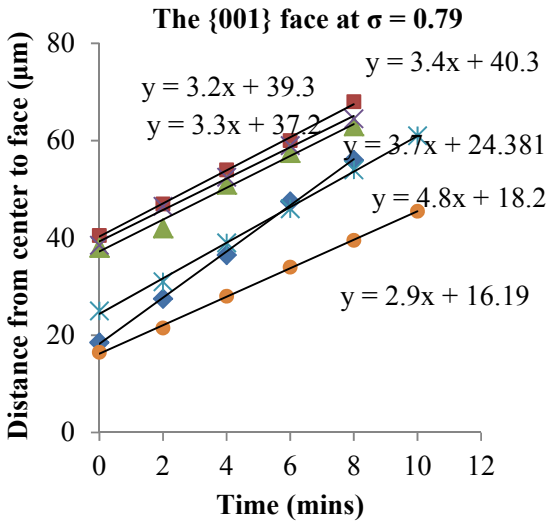

The {011} face at σ = 0.93
Distance from center to face (µm)
Time (mins)
y = 71x + 839.67
y = 61.3x + 855.3
y = 55.7x + 263.4
y = 55.7x + 263.4
y = 55.5x + 369.5


The {001} face at σ = 0.93
Distant from cneter to face (µm)
Time (mins)
y = 5.1x + 100.1
y = 5.5x + 57.667
y = 4.6x + 38.85
y = 4.8x + 35.35
y = 4.9x + 33.15

σ = 0.79

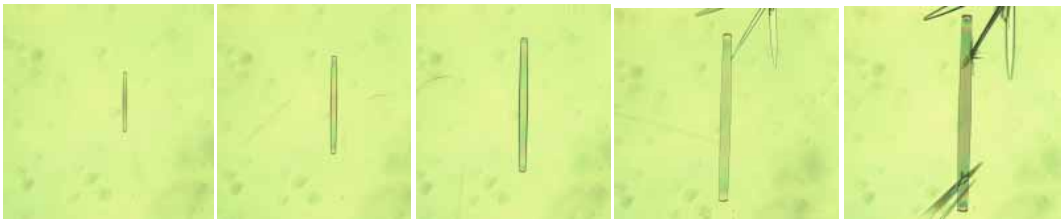


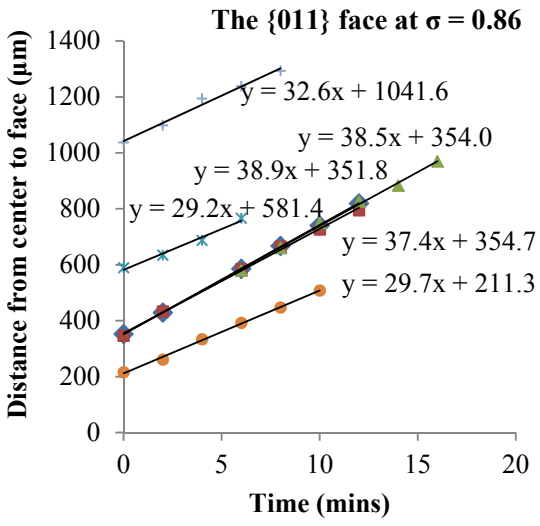


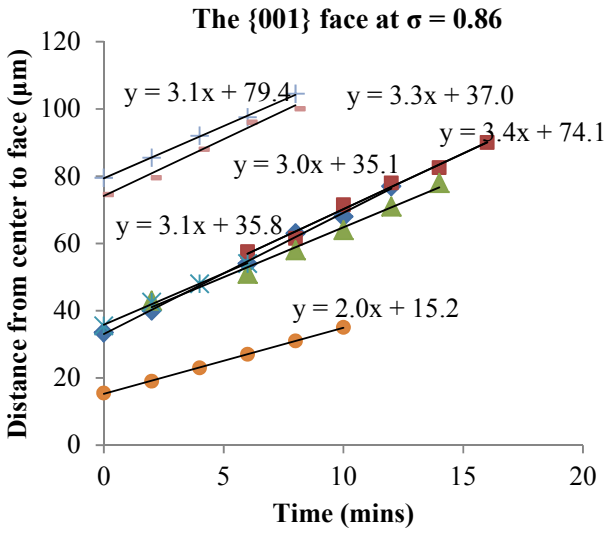


S2.1.4 Toluene Solutions

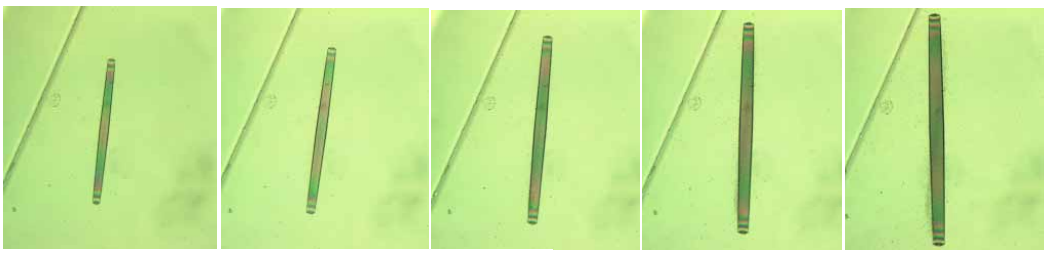
σ = 0.86

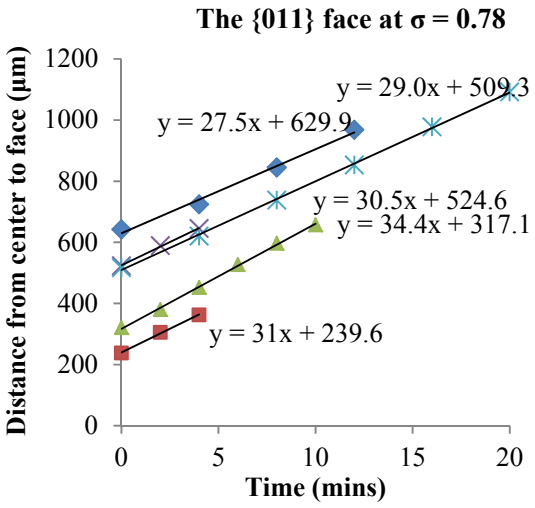


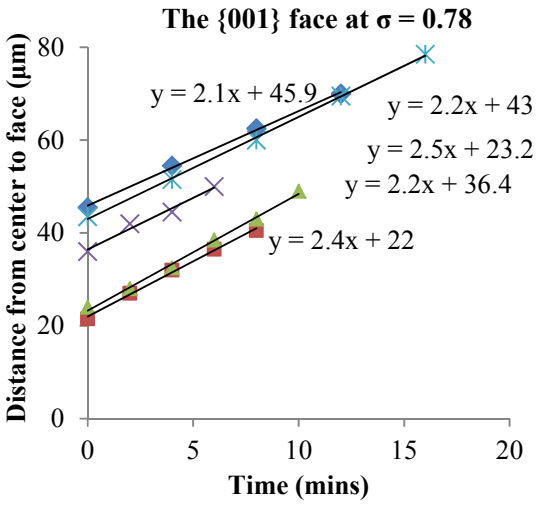




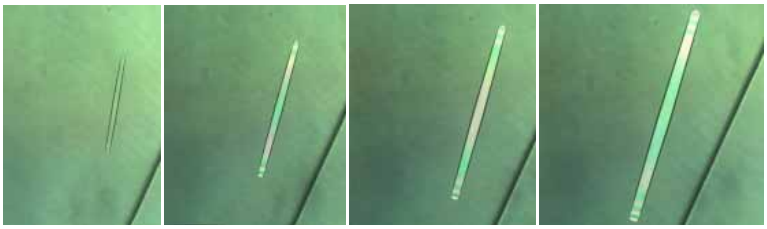
σ = 0.78

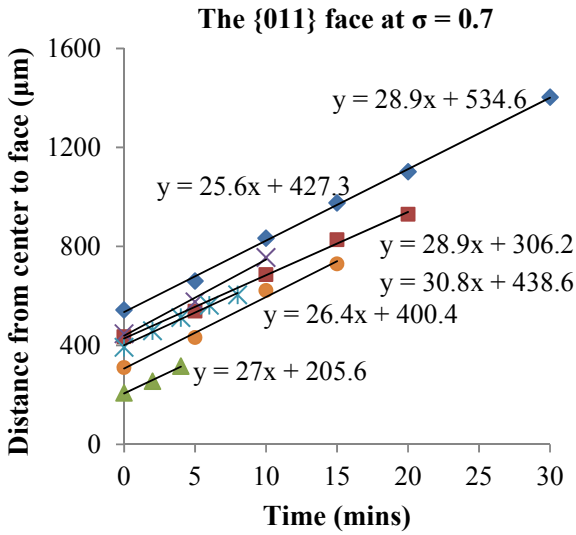


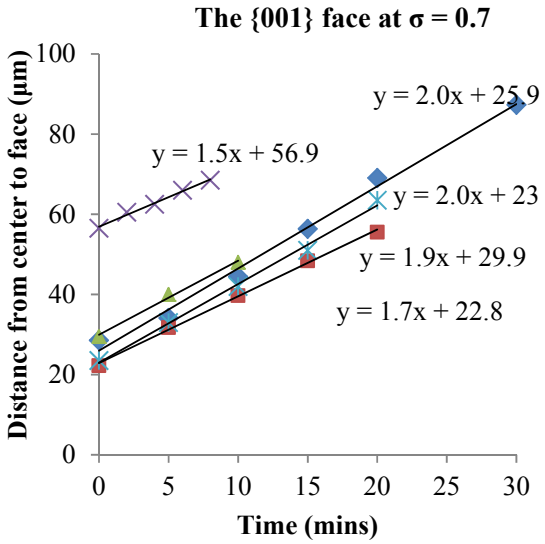

The {011} face at σ = 0.78
Distance from center to face (µm)
Time (mins)
y = 29.0x + 509.3
y = 27.5x + 629.9
y = 30.5x + 524.6
y = 34.4x + 317.1
y = 31x + 239.6
0
200
400
600
800
1000
1200
0
5
10
15
20


The {001} face at σ = 0.78
Distance from center to face (µm)
Time (mins)
y = 2.1x + 45.9
y = 2.2x + 43
y = 2.5x + 23.2
y = 2.2x + 36.4
y = 2.4x + 22
0
20
40
60
80
0
5
10
15
20

σ = 0.70



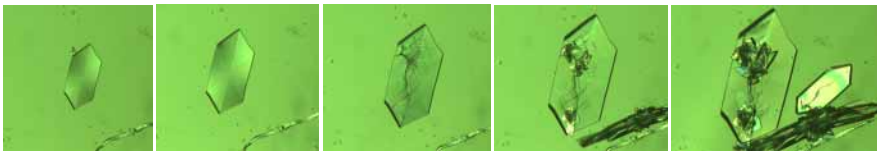

The {011} face at σ = 0.7
Distance from center to face (µm)
Time (mins)
y = 28.9x + 534.6
y = 25.6x + 427.3
y = 28.9x + 306.2
y = 30.8x + 438.6
y = 26.4x + 400.4
y = 27x + 205.6
0
400
800
1200
1600
0
5
10
15
20
25
30

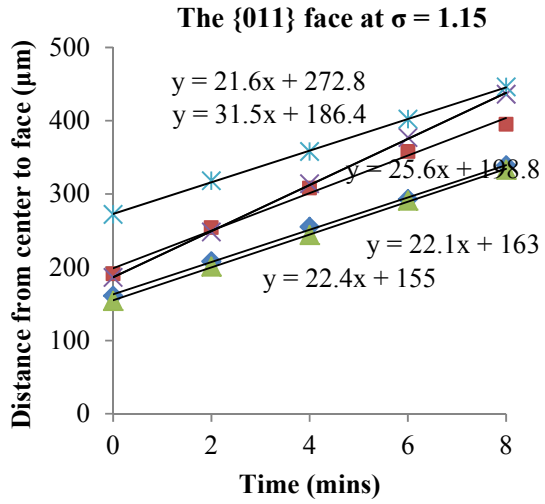

The {001} face at σ = 0.7
Distance from center to face (µm)
Time (mins)
y = 2.0x + 25.9
y = 1.5x + 56.9
y = 2.0x + 23
y = 1.9x + 29.9
y = 1.7x + 22.8
0
20
40
60
80
100
0
5
10
15
20
25
30

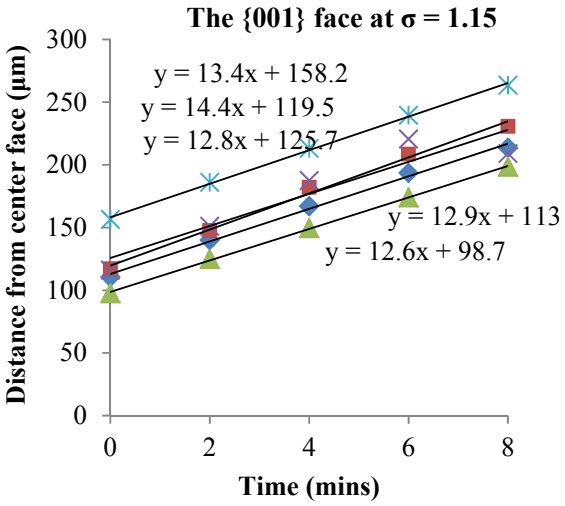
S2.2 Data from the 15ml jacketed vessel

S2.2.1 95% Ethanol /Water Solutions

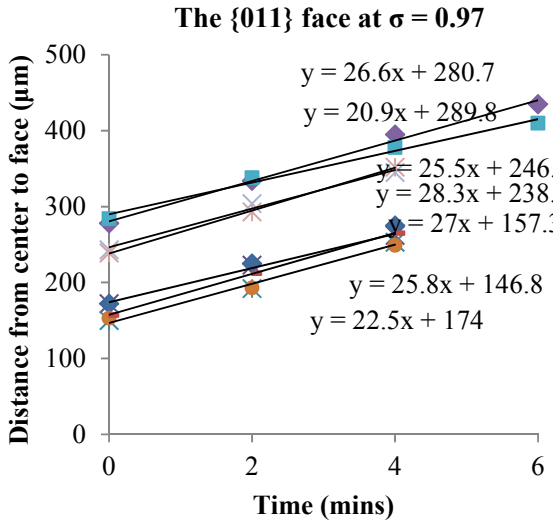
σ = 1.15

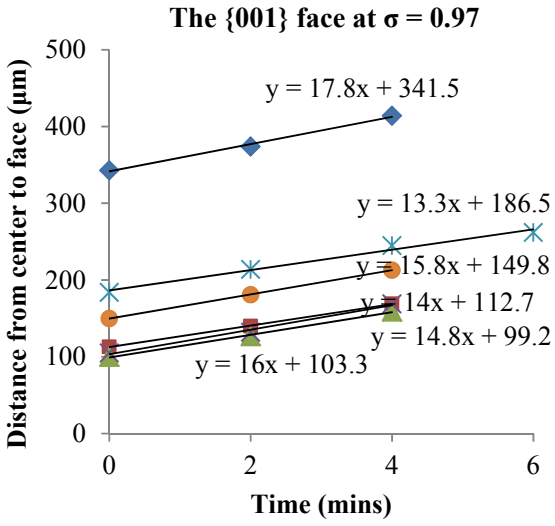




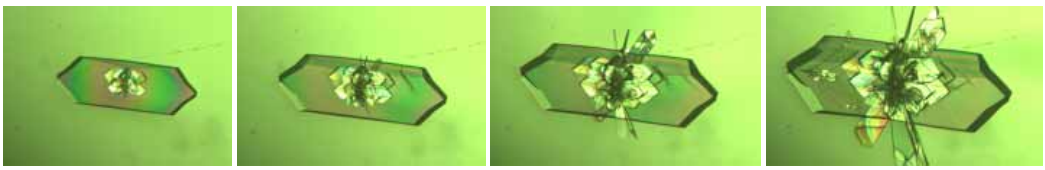


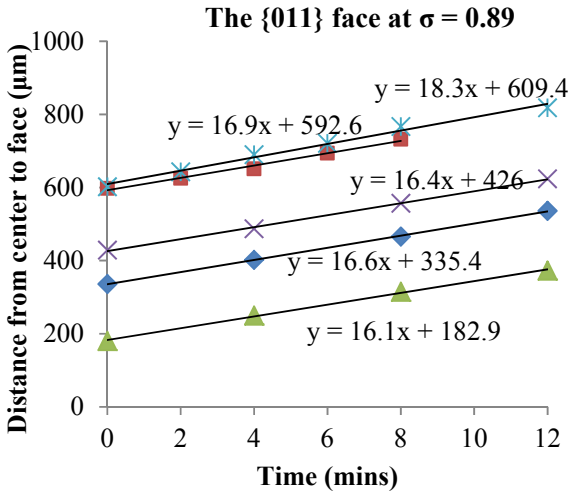
σ = 0.97

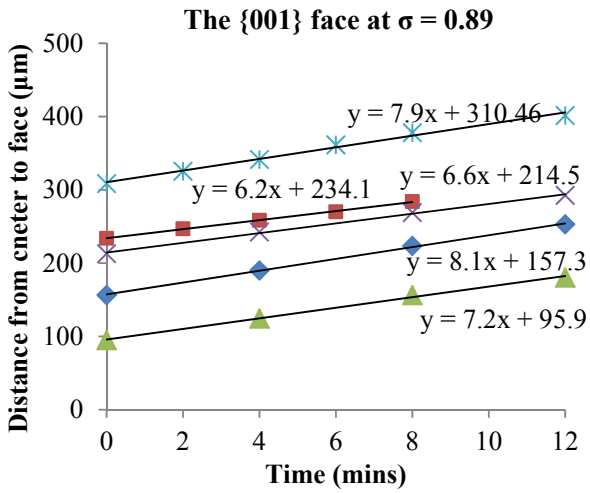




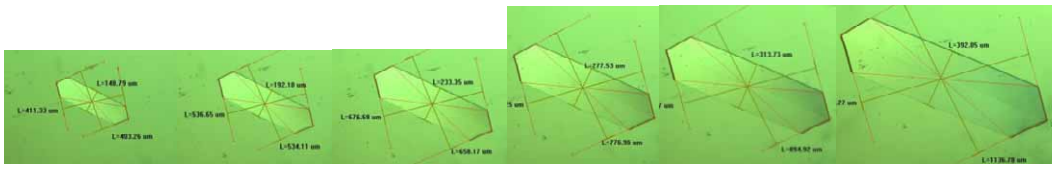
σ = 0.89

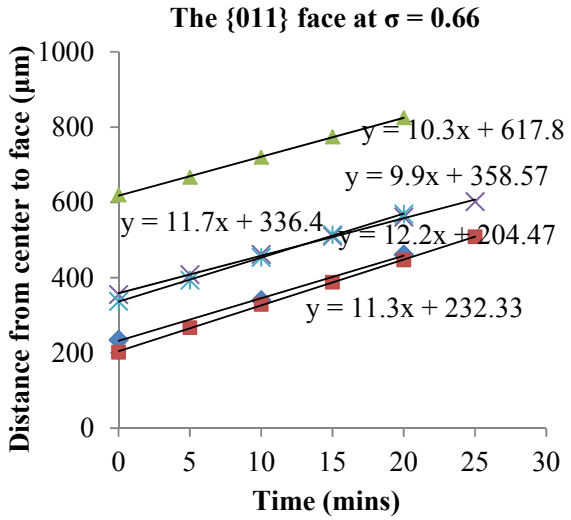


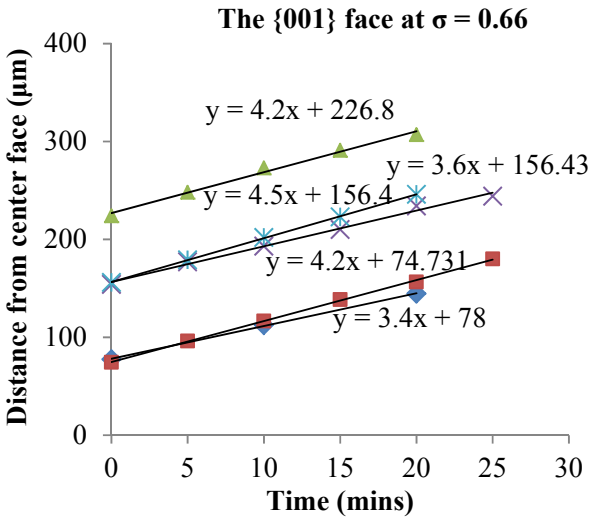

The {011} face at σ = 0.89
Distance from center to face (µm)
Time (mins)
y = 18.3x + 609.4
y = 16.9x + 592.6
y = 16.4x + 426
y = 16.6x + 335.4
y = 16.1x + 182.9


The {001} face at σ = 0.89
Distance from cneter to face (µm)
Time (mins)
y = 7.9x + 310.46
y = 6.2x + 234.1
y = 6.6x + 214.5
y = 8.1x + 157.3
y = 7.2x + 95.9

σ = 0.66

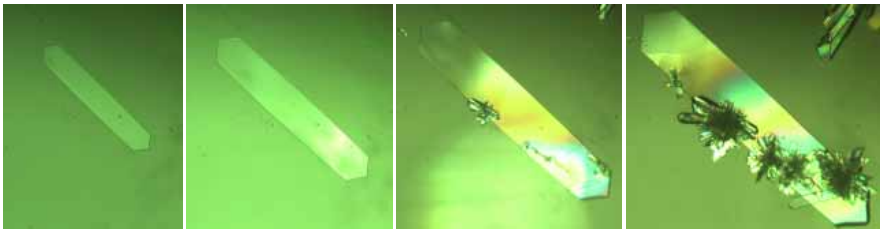


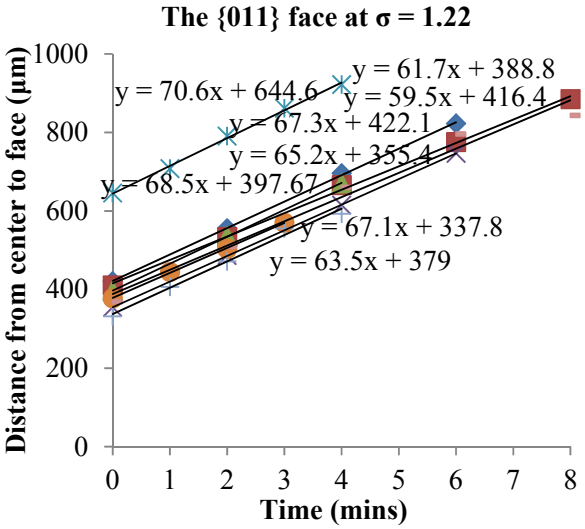

The {011} face at σ = 0.66
Distance from center to face (µm)
Time (mins)
y = 10.3x + 617.8
y = 9.9x + 358.57
y = 11.7x + 336.4
y = 12.2x + 204.47
y = 11.3x + 232.33

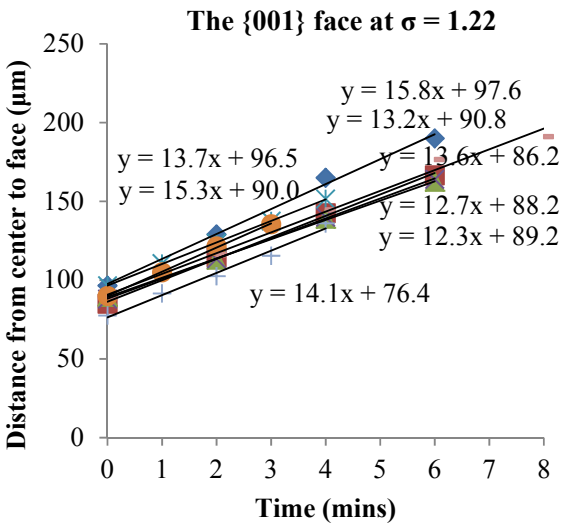

The {001} face at σ = 0.66
Distance from center face (µm)
Time (mins)
y = 4.2x + 226.8
y = 3.6x + 156.43
y = 4.5x + 156.4
y = 4.2x + 74.731
y = 3.4x + 78

S2.2.2 Ethyl Acetate Solutions

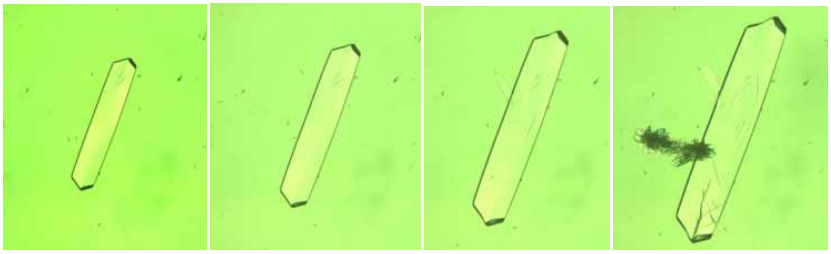
σ = 1.22

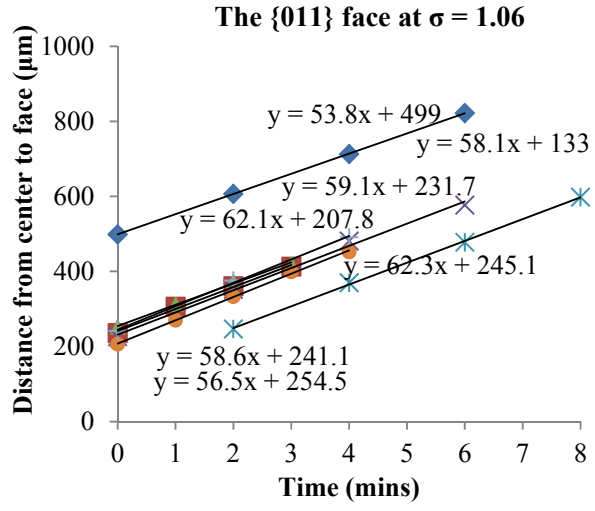


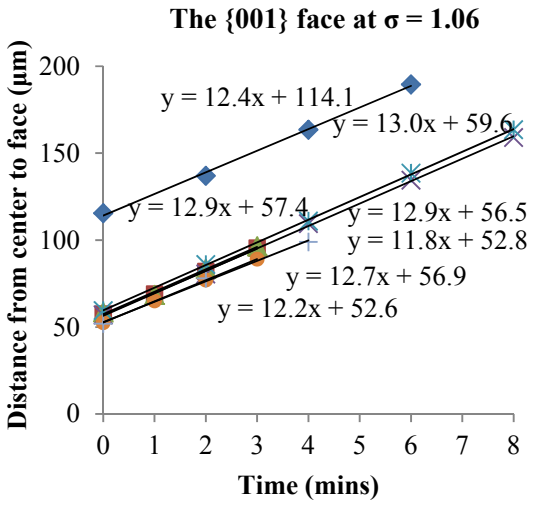




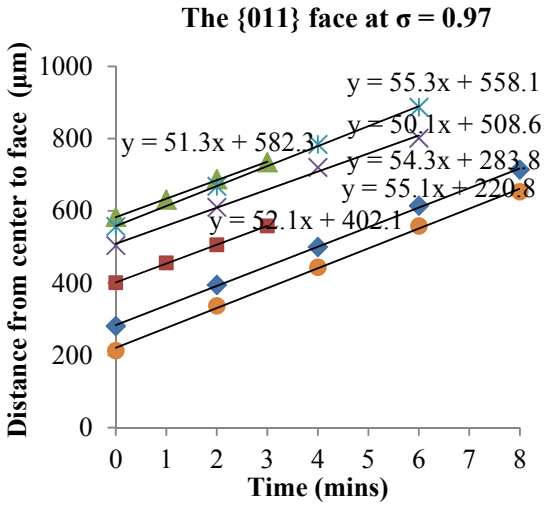
σ = 1.06

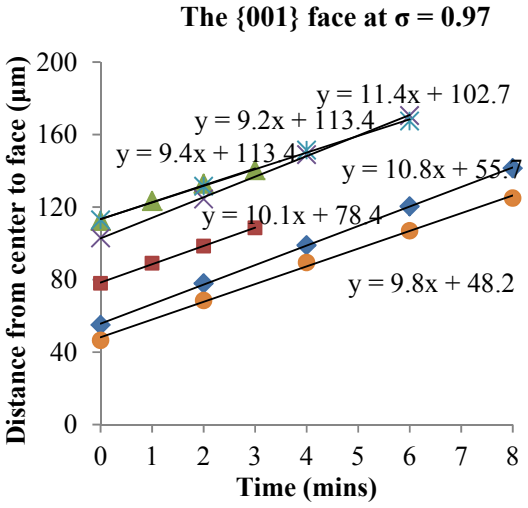




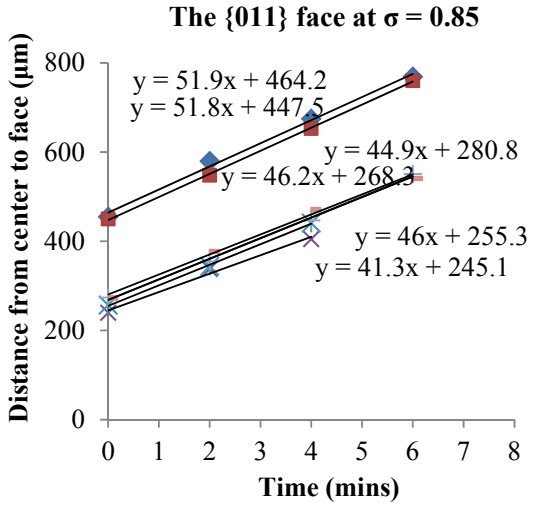


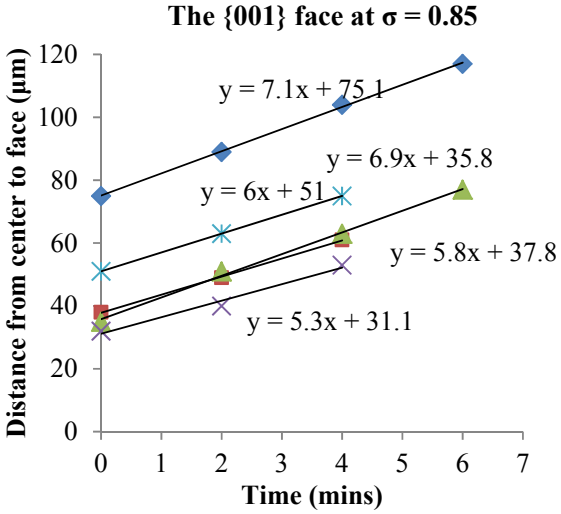
σ = 0.97


The {011} face at σ = 0.97
Distance from center to face (µm)
Time (mins)
y = 55.3x + 558.1
y = 50.1x + 508.6
y = 54.3x + 283.8
y = 55.1x + 220.8
y = 51.3x + 582.3
y = 52.1x + 402.1

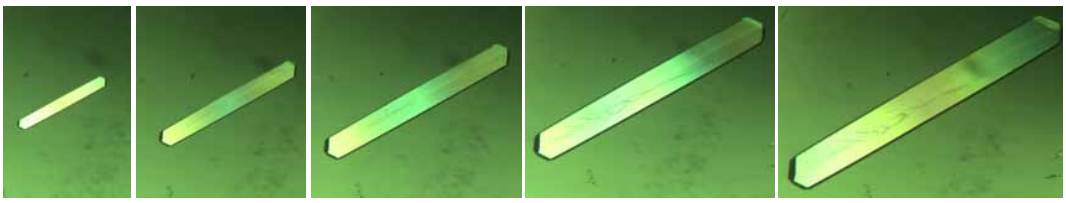

The {001} face at σ = 0.97
Distance from center to face (µm)
Time (mins)
y = 11.4x + 102.7
y = 9.2x + 113.4
y = 9.4x + 113.4
y = 10.8x + 55.7
y = 10.1x + 78.4
y = 9.8x + 48.2

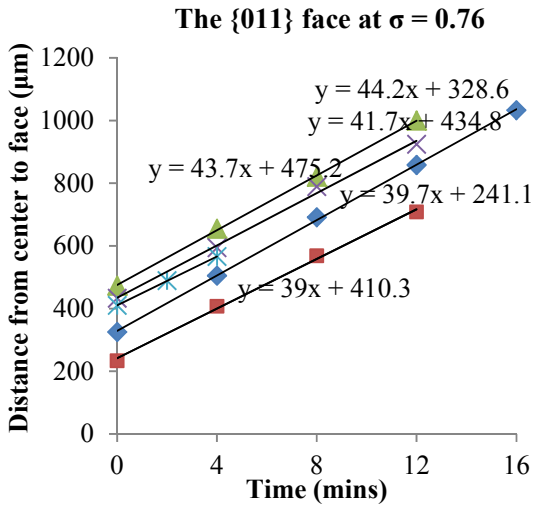
σ = 0.85

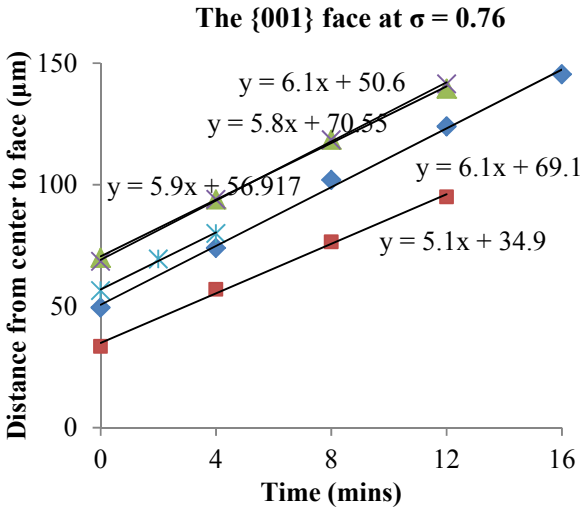

The {011} face at σ = 0.85
Distance from center to face (µm)
Time (mins)
y = 51.9x + 464.2
y = 51.8x + 447.5
y = 44.9x + 280.8
y = 46.2x + 268.3
y = 46x + 255.3
y = 41.3x + 245.1


The {001} face at σ = 0.85
Distance from center to face (µm)
Time (mins)
y = 7.1x + 75.1
y = 6.9x + 35.8
y = 6x + 51
y = 5.8x + 37.8
y = 5.3x + 31.1

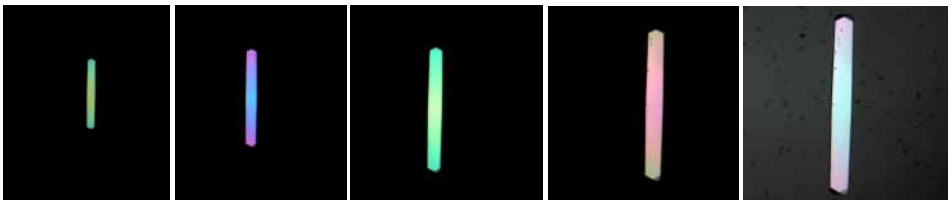
σ = 0.76

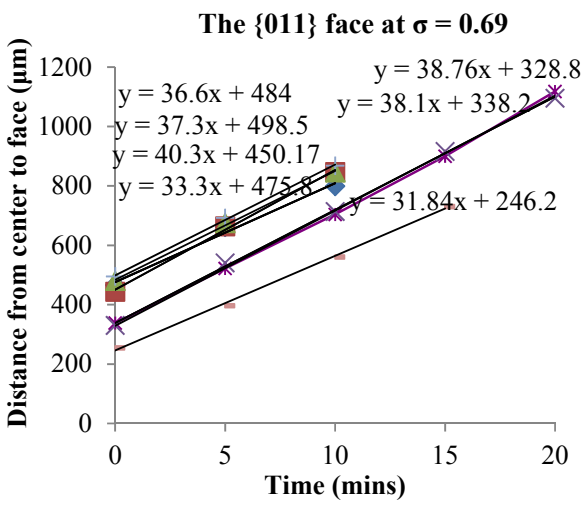


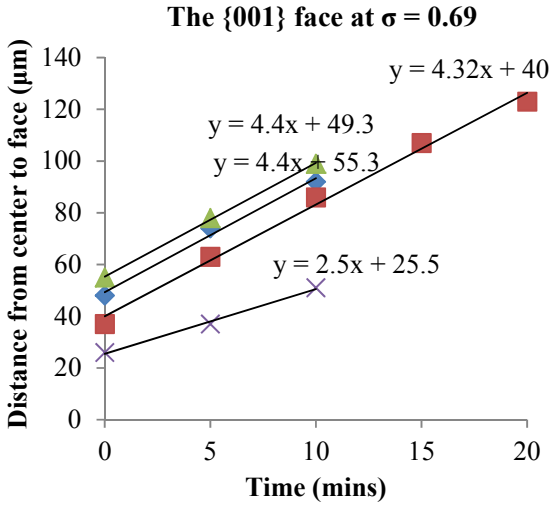

The {011} face at σ = 0.76
Distance from center to face (µm)
Time (mins)
y = 44.2x + 328.6
y = 41.7x + 434.8
y = 43.7x + 475.2
y = 39.7x + 241.1
y = 39x + 410.3
0
200
400
600
800
1000
1200
0
4
8
12
16


The {001} face at σ = 0.76
Distance from center to face (µm)
Time (mins)
y = 6.1x + 50.6
y = 5.8x + 70.55
y = 5.9x + 56.917
y = 6.1x + 69.1
y = 5.1x + 34.9
0
50
100
150
0
4
8
12
16

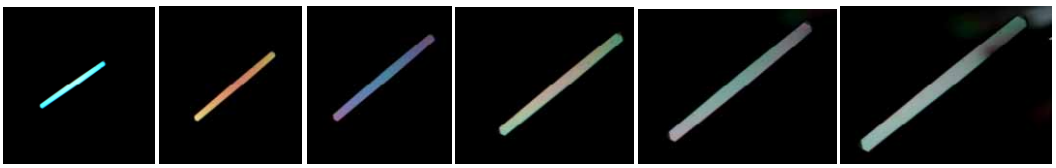
σ = 0.69

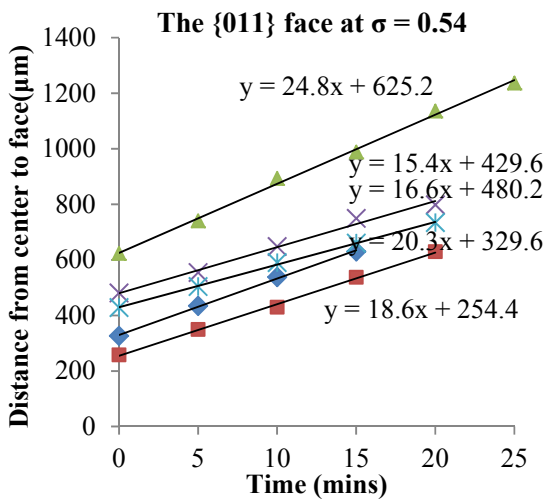


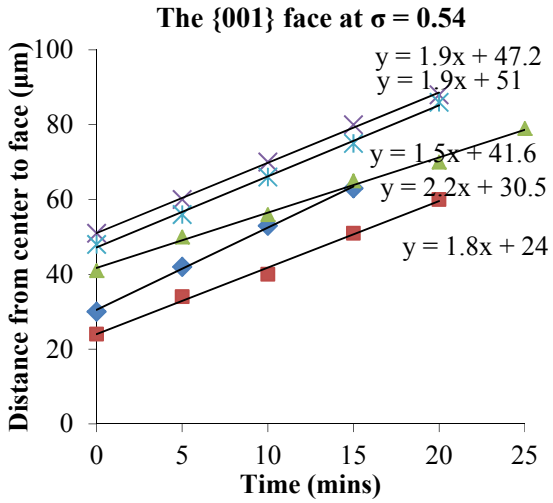

The {011} face at σ = 0.69
Distance from center to face (µm)
Time (mins)
y = 38.76x + 328.8
y = 38.1x + 338.2
y = 36.6x + 484
y = 37.3x + 498.5
y = 40.3x + 450.17
y = 33.3x + 475.8
y = 31.84x + 246.2
0
200
400
600
800
1000
1200
0
5
10
15
20


The {001} face at σ = 0.69
Distance from center to face (µm)
Time (mins)
y = 4.32x + 40
y = 4.4x + 49.3
y = 4.4x + 55.3
y = 2.5x + 25.5
0
20
40
60
80
100
120
140
0
5
10
15
20

σ = 0.54

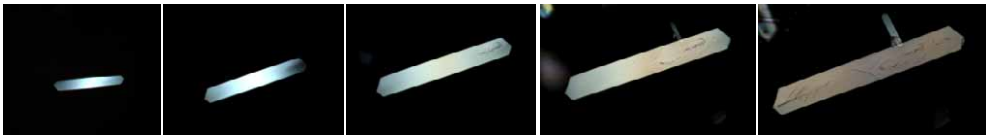


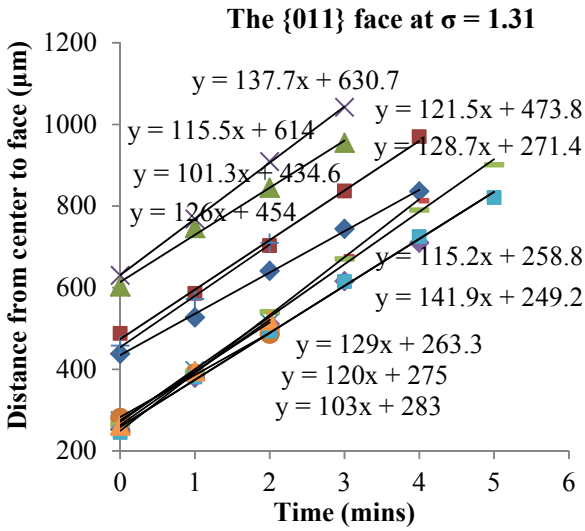


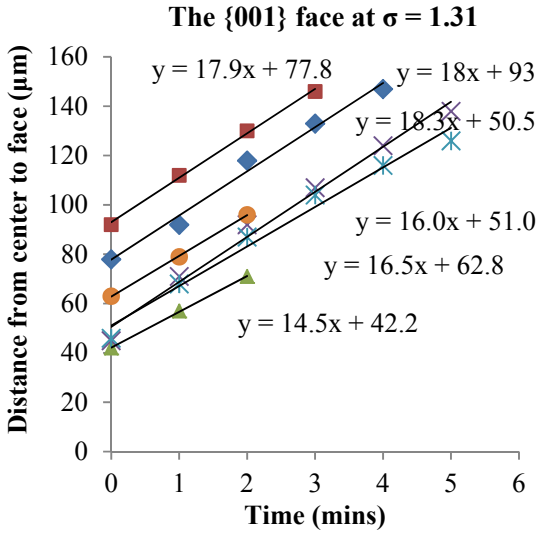


S2.2.3 Acetonitrile Solutions

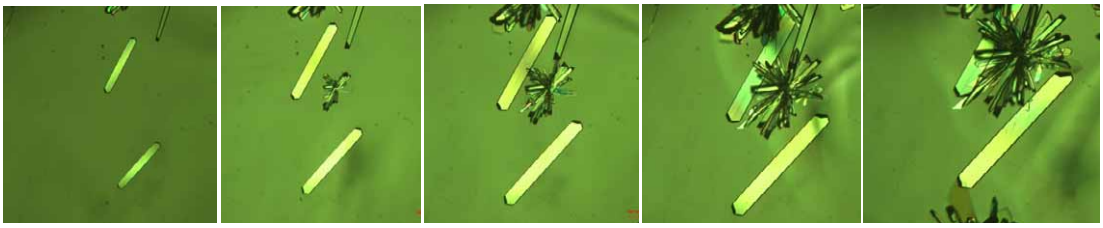
σ = 1.31

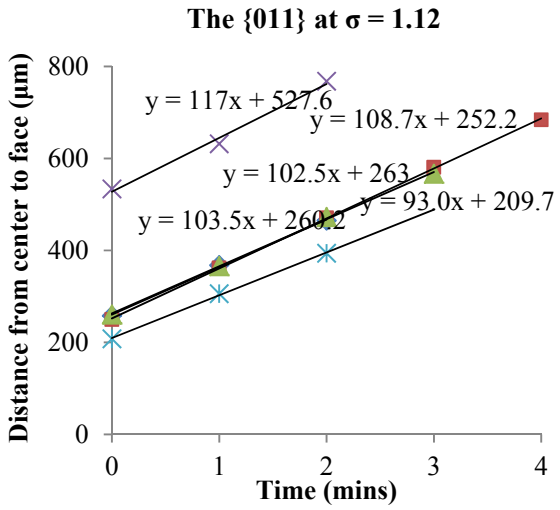


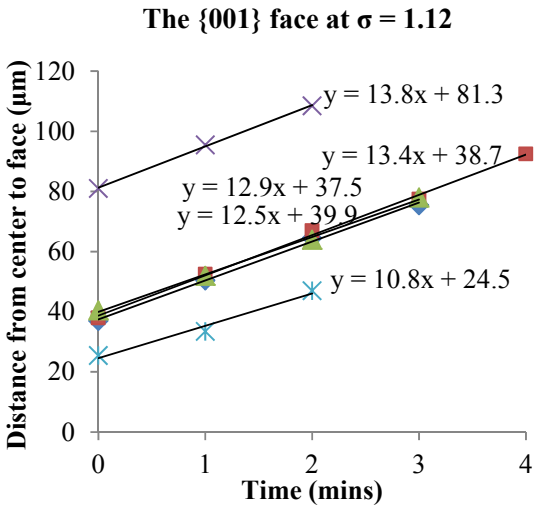




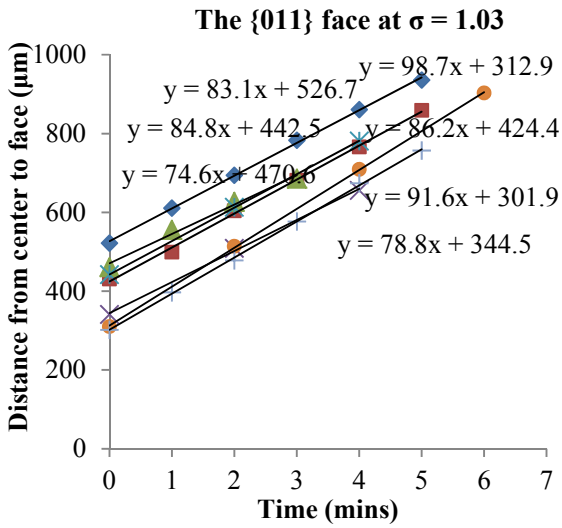
σ = 1.12

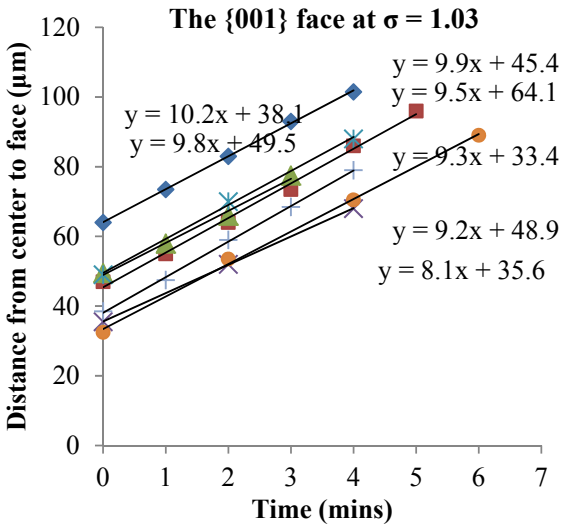



The {011} at σ = 1.12
Distance from center to face (µm)
Time (mins)
y = 117x + 527.6
y = 108.7x + 252.2
y = 102.5x + 263
y = 103.5x + 260.2
y = 93.0x + 209.7

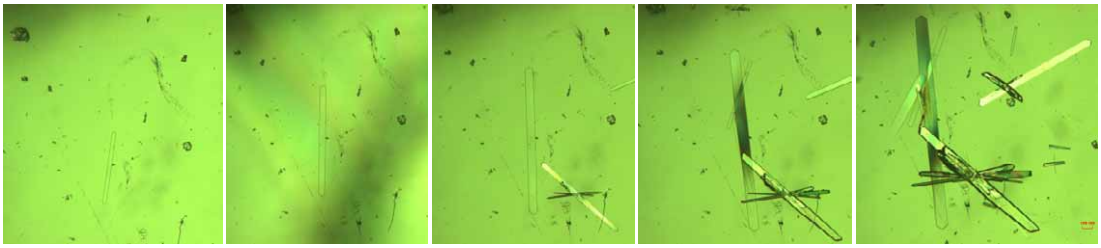

The {001} face at σ = 1.12
Distance from center to face (µm)
Time (mins)
y = 13.8x + 81.3
y = 13.4x + 38.7
y = 12.9x + 37.5
y = 12.5x + 39.9
y = 10.8x + 24.5

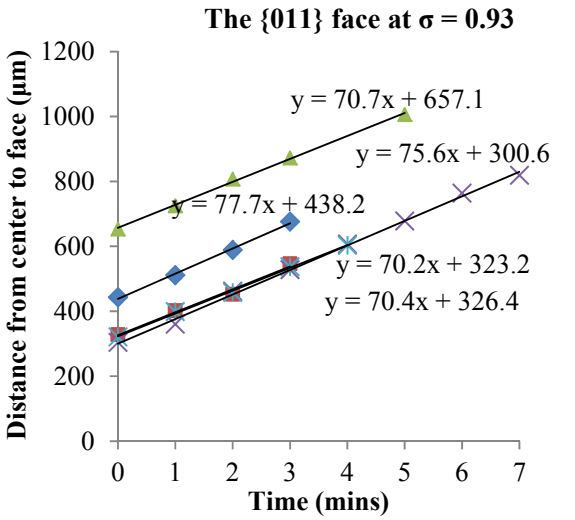
σ = 1.03

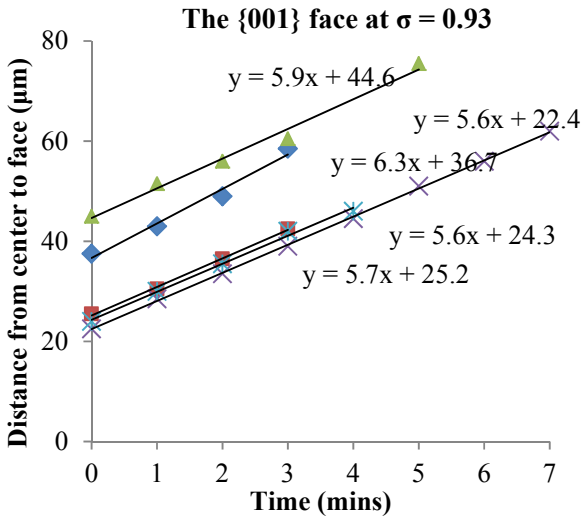

The {011} face at σ = 1.03
Distance from center to face (µm)
Time (mins)
y = 98.7x + 312.9
y = 83.1x + 526.7
y = 84.8x + 442.5
y = 86.2x + 424.4
y = 74.6x + 470.6
y = 91.6x + 301.9
y = 78.8x + 344.5


The {001} face at σ = 1.03
Distance from center to face (µm)
Time (mins)
y = 9.9x + 45.4
y = 9.5x + 64.1
y = 10.2x + 38.1
y = 9.8x + 49.5
y = 9.3x + 33.4
y = 9.2x + 48.9
y = 8.1x + 35.6

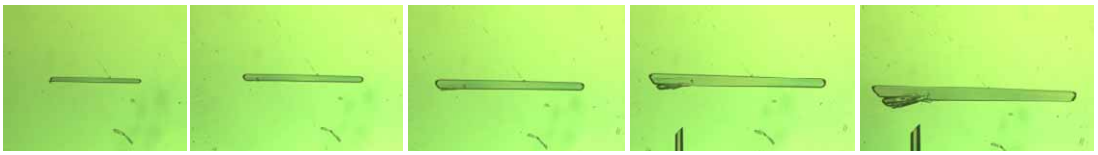
σ = 0.93

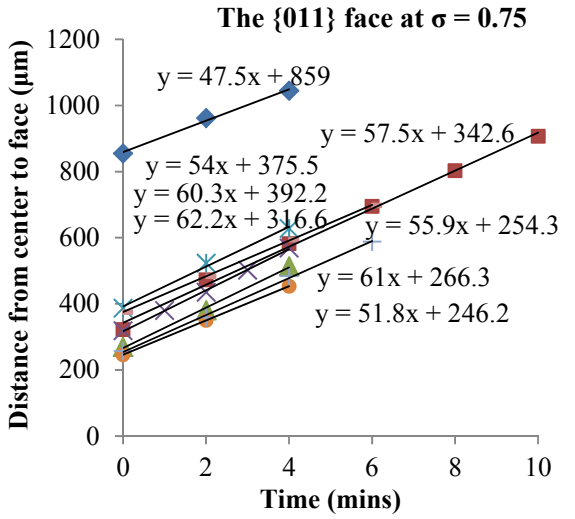


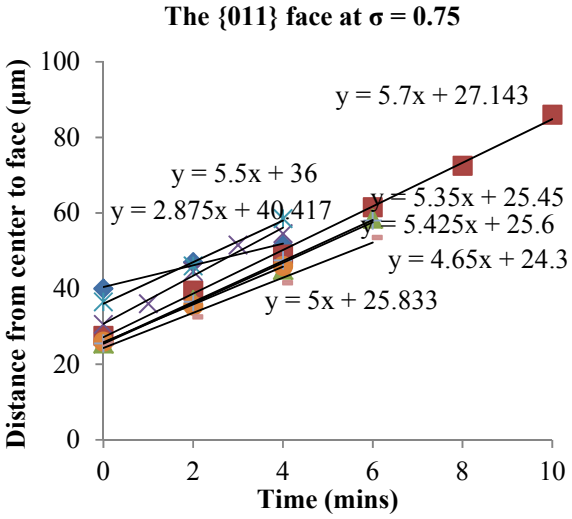

The {011} face at σ = 0.93
Distance from center to face (µm)
Time (mins)
y = 70.7x + 657.1
y = 75.6x + 300.6
y = 77.7x + 438.2
y = 70.2x + 323.2
y = 70.4x + 326.4


The {001} face at σ = 0.93
Distance from center to face (µm)
Time (mins)
y = 5.9x + 44.6
y = 5.6x + 22.4
y = 6.3x + 36.7
y = 5.6x + 24.3
y = 5.7x + 25.2

σ = 0.75

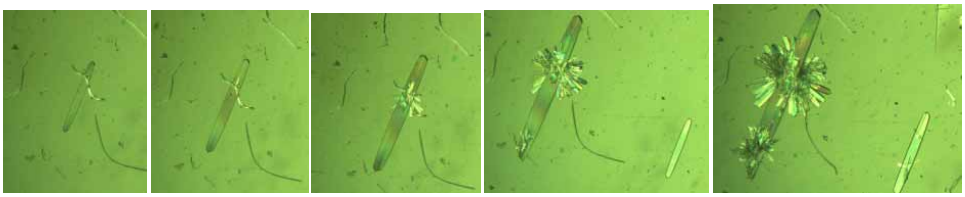


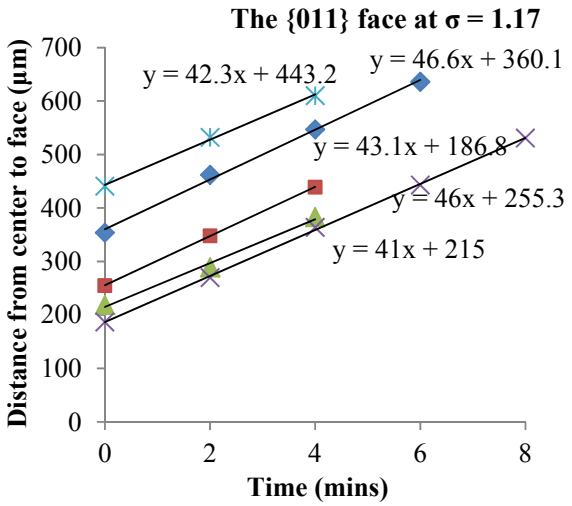

The {011} face at σ = 0.75
Distance from center to face (µm)
Time (mins)
y = 47.5x + 859
y = 57.5x + 342.6
y = 54x + 375.5
y = 60.3x + 392.2
y = 62.2x + 316.6
y = 55.9x + 254.3
y = 61x + 266.3
y = 51.8x + 246.2

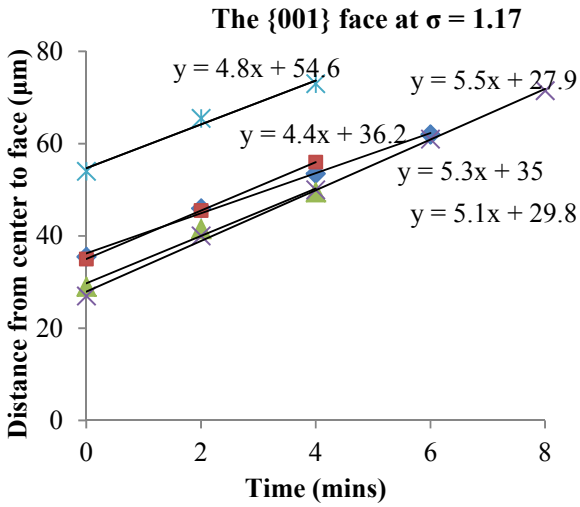

The {011} face at σ = 0.75
Distance from center to face (µm)
Time (mins)
y = 5.7x + 27.143
y = 5.5x + 36
y = 2.875x + 40.417
y = 5.35x + 25.45
y = 5.425x + 25.6
y = 4.65x + 24.3
y = 5x + 25.833

S2.2.4 Toluene Solutions

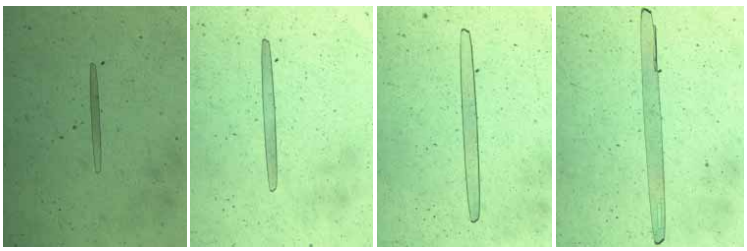
σ = 1.17

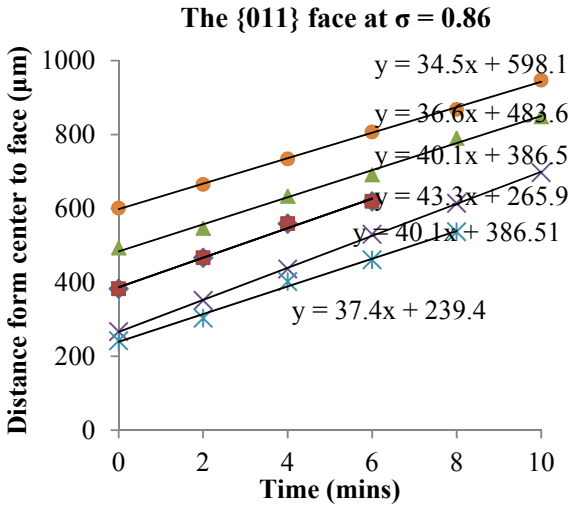


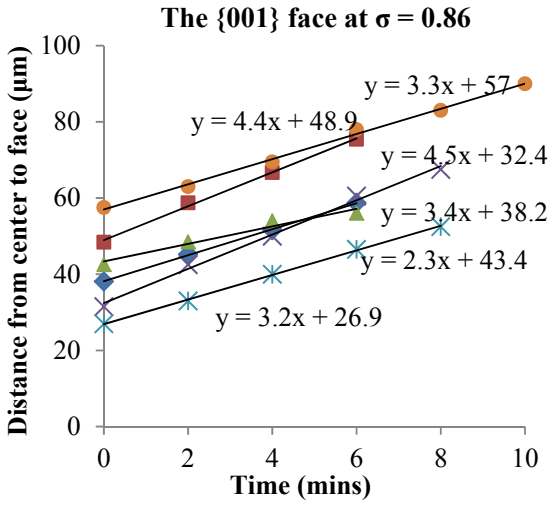




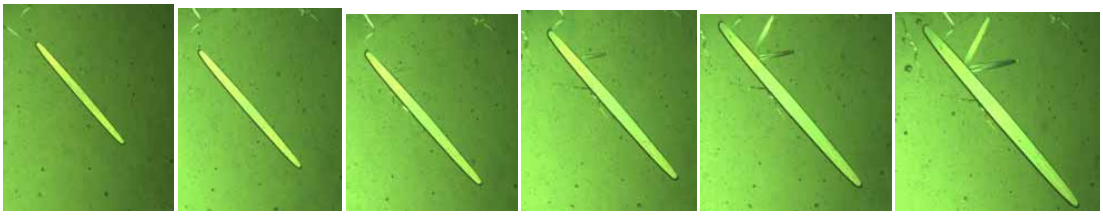
σ = 0.86

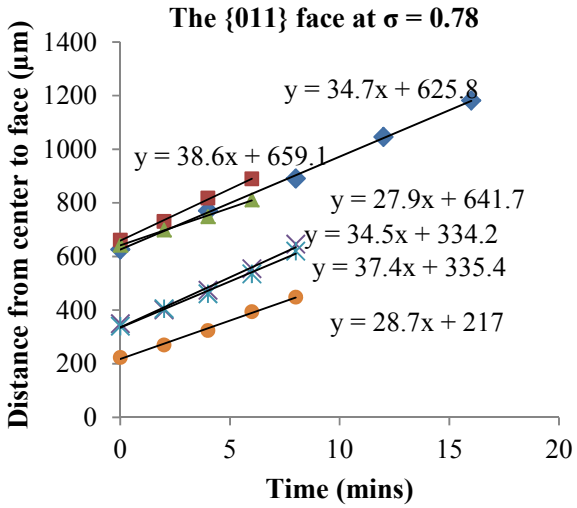


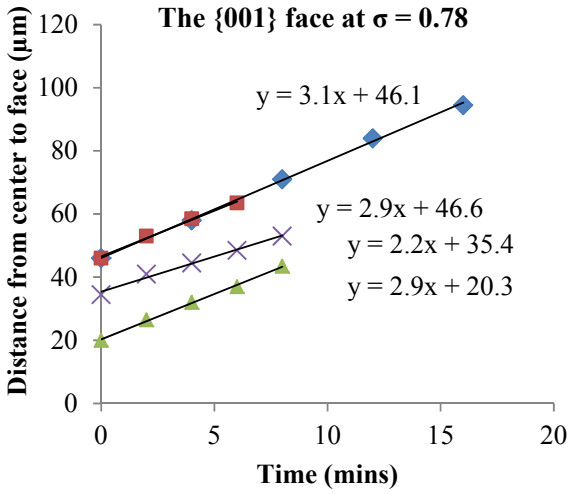




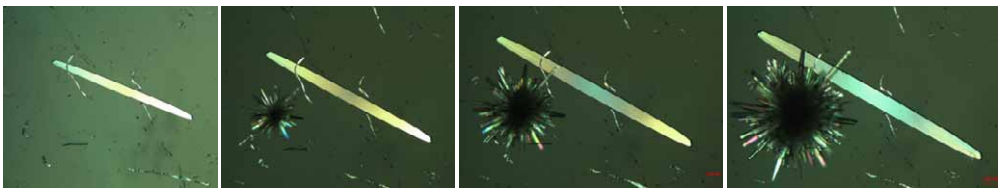
σ = 0.78

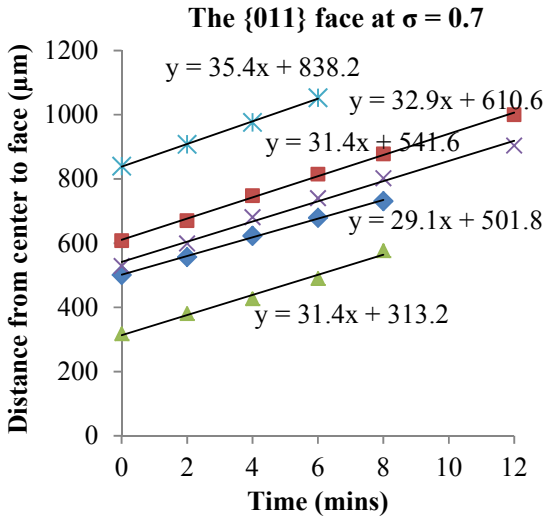


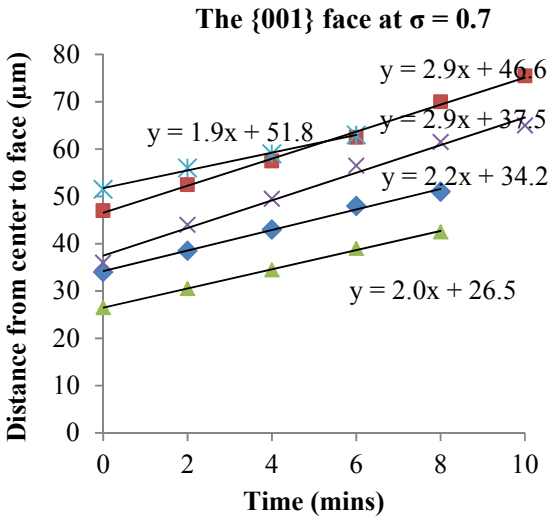

The {011} face at σ = 0.78
Distance from center to face (µm)
Time (mins)
y = 34.7x + 625.8
y = 38.6x + 659.1
y = 27.9x + 641.7
y = 34.5x + 334.2
y = 37.4x + 335.4
y = 28.7x + 217


The {001} face at σ = 0.78
Distance from center to face (µm)
Time (mins)
y = 3.1x + 46.1
y = 2.9x + 46.6
y = 2.2x + 35.4
y = 2.9x + 20.3

σ = 0.70




The {011} face at σ = 0.7
Distance from center to face (µm)
Time (mins)
y = 35.4x + 838.2
y = 32.9x + 610.6
y = 31.4x + 541.6
y = 29.1x + 501.8
y = 31.4x + 313.2


The {001} face at σ = 0.7
Distance from center to face (µm)
Time (mins)
y = 2.9x + 46.6
y = 2.9x + 37.5
y = 1.9x + 51.8
y = 2.2x + 34.2
y = 2.0x + 26.5