

Supplementary Information

Spontaneous cocrystal hydrate formation in the solid state: crystal structure aspects and kinetics

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Table S1 Selected hydrogen bonds in 4-aminosalicylic acid–nicotinamide cocrystal

| | Symmetry code | D–H (°) | H···A (°) | D···A (°) | ∠D–H···A (°) |
|---------------|------------------------|---------|-----------|-----------|--------------|
| O10–H10···N1 | x, y, z | 0.96(2) | 1.69(2) | 2.644(1) | 171(2) |
| N9–H9A···O8 | $-2 -x, -y, -z$ | 0.90(2) | 2.11(2) | 2.996(2) | 169.2(2) |
| N20–H20A···O8 | $2 +x, 0.5 -y, 0.5 +z$ | 0.92(2) | 2.18(2) | 2.77(2) | 145.2(2) |

Table S2 Results of conventional solid state kinetic model fitting to hydration of anhydrous 4-aminosalicylic acid–nicotinamide cocrystal

| Model | RH (%) | | | |
|-------|----------------|-------|-------|-------|
| | 40 | 50 | 70 | 80 |
| | R ² | | | |
| P2 | 0.833 | 0.722 | 0.732 | 0.517 |
| P3 | 0.901 | 0.798 | 0.773 | 0.614 |
| P4 | 0.777 | 0.667 | 0.704 | 0.451 |
| A2 | 0.892 | 0.830 | 0.848 | 0.762 |
| A3 | 0.955 | 0.910 | 0.844 | 0.880 |
| A4 | 0.845 | 0.776 | 0.815 | 0.679 |
| R2 | 0.931 | 0.858 | 0.842 | 0.755 |
| R3 | 0.940 | 0.877 | 0.863 | 0.801 |
| D1 | 0.971 | 0.903 | 0.843 | 0.755 |
| D2 | 0.982 | 0.936 | 0.890 | 0.839 |
| D3 | 0.916 | 0.822 | 0.791 | 0.649 |
| D4 | 0.985 | 0.948 | 0.908 | 0.874 |
| F1 | 0.955 | 0.910 | 0.902 | 0.880 |
| F2 | 0.988 | 0.979 | 0.978 | 0.995 |
| F3 | 0.994 | 0.999 | 0.999 | 0.968 |

Table S3 Results of conventional solid state kinetic model fitting for the formation of 4-aminosalicylic acid–nicotinamide cocrystal monohydrate from starting components

| Model | RH, % | | |
|-------|----------------|-------|-------|
| | 70 | 80 | 90 |
| | R ² | | |
| P2 | 0.837 | 0.809 | 0.566 |
| P3 | 0.933 | 0.891 | 0.629 |
| P4 | 0.747 | 0.743 | 0.524 |
| A2 | 0.848 | 0.833 | 0.638 |
| A3 | 0.941 | 0.914 | 0.717 |
| A4 | 0.777 | 0.779 | 0.595 |
| R2 | 0.937 | 0.903 | 0.674 |
| R3 | 0.939 | 0.906 | 0.689 |
| D1 | 0.991 | 0.976 | 0.742 |
| D2 | 0.992 | 0.981 | 0.775 |
| D3 | 0.937 | 0.900 | 0.650 |
| D4 | 0.992 | 0.982 | 0.788 |
| F1 | 0.941 | 0.914 | 0.717 |
| F2 | 0.950 | 0.934 | 0.795 |
| F3 | 0.957 | 0.952 | 0.860 |

Table S4 Rietveld analysis of kinetic data for the hydration of anhydrous 4-aminosalicylic acid–nicotinamide cocrystal at 40% RH, 30 °C

| Time, min | W _{hydrate} , % | W _{cocrystal} , % | Rwp |
|-----------|--------------------------|----------------------------|-------|
| 3.0 | 7.0 | 93.0 | 7.80 |
| 9.0 | 11.8 | 88.2 | 7.13 |
| 14.0 | 16.3 | 83.3 | 6.27 |
| 24.0 | 21.9 | 78.1 | 5.80 |
| 30.0 | 28.9 | 71.1 | 5.65 |
| 37.0 | 33.7 | 66.3 | 5.58 |
| 43.0 | 37.0 | 63.0 | 6.09 |
| 58.0 | 42.5 | 57.5 | 6.12 |
| 63.0 | 46.9 | 53.1 | 6.41 |
| 71.0 | 49.1 | 50.9 | 6.65 |
| 77.0 | 51.1 | 49.0 | 7.00 |
| 80.0 | 51.4 | 48.6 | 7.75 |
| 86.0 | 53.1 | 46.9 | 6.81 |
| 89.0 | 53.5 | 46.5 | 7.81 |
| 97.0 | 55.6 | 44.4 | 6.88 |
| 103.0 | 56.7 | 43.3 | 7.07 |
| 111.0 | 56.7 | 43.3 | 10.30 |
| 119.0 | 59.3 | 40.7 | 9.59 |
| 126.0 | 60.3 | 39.7 | 7.51 |
| 138.0 | 61.9 | 38.1 | 7.51 |
| 146.0 | 62.1 | 37.9 | 7.60 |

Table S5 Rietveld analysis of kinetic data for the hydration of anhydrous 4-aminosalicylic acid–nicotinamide cocrystal at 50% RH, 30 °C

| Time, min | W _{hydrate} , % | W _{cocrystal} , % | Rwp |
|-----------|--------------------------|----------------------------|-------|
| 2.7 | 15.0 | 85.0 | 7.79 |
| 8.0 | 25.7 | 74.3 | 8.53 |
| 13.2 | 34.3 | 65.7 | 9.12 |
| 18.5 | 41.2 | 58.8 | 9.95 |
| 23.7 | 46.4 | 53.7 | 10.09 |
| 28.9 | 50.8 | 49.3 | 10.98 |
| 34.2 | 53.8 | 46.2 | 11.03 |
| 39.4 | 56.7 | 43.4 | 11.45 |
| 44.7 | 59.2 | 40.8 | 11.63 |
| 49.9 | 61.0 | 39.1 | 11.67 |
| 55.2 | 62.7 | 37.3 | 11.75 |
| 60.4 | 64.4 | 35.6 | 12.22 |
| 65.7 | 65.6 | 34.4 | 12.28 |
| 70.9 | 66.6 | 33.4 | 11.95 |
| 76.1 | 67.9 | 32.1 | 12.23 |
| 81.4 | 68.9 | 31.1 | 12.53 |
| 86.6 | 69.5 | 30.5 | 12.53 |
| 91.9 | 70.5 | 29.5 | 12.53 |
| 97.1 | 71.4 | 28.7 | 12.74 |
| 107.6 | 72.2 | 27.8 | 12.82 |
| 118.1 | 73.7 | 26.3 | 12.87 |
| 128.5 | 74.9 | 25.1 | 12.88 |

Table S6 Rietveld analysis of kinetic data for the hydration of anhydrous 4-aminosalicylic acid–nicotinamide cocrystal at 70% RH, 30 °C

| Time, min | W _{hydrate} , % | W _{cocrystal} , % | Rwp |
|-----------|--------------------------|----------------------------|-------|
| 2.6 | 39.7 | 60.3 | 9.59 |
| 5.1 | 52.3 | 47.7 | 10.70 |
| 7.6 | 59.3 | 40.7 | 11.67 |
| 10.1 | 64.1 | 35.9 | 11.95 |
| 12.6 | 67.9 | 32.1 | 12.37 |
| 15.1 | 70.9 | 29.1 | 12.33 |
| 17.6 | 73.2 | 26.8 | 12.85 |
| 20.1 | 74.5 | 25.5 | 13.06 |
| 22.6 | 75.9 | 24.1 | 12.91 |
| 25.0 | 77.0 | 23.0 | 13.12 |
| 30.0 | 79.4 | 20.6 | 13.31 |
| 32.5 | 80.0 | 20.0 | 13.49 |
| 35.0 | 80.8 | 19.2 | 13.35 |
| 40.0 | 81.8 | 18.2 | 13.67 |
| 42.5 | 82.4 | 17.7 | 13.65 |
| 45.0 | 82.9 | 17.1 | 13.47 |

Table S7 Rietveld analysis of kinetic data for the hydration of anhydrous 4-aminosalicylic acid–nicotinamide cocrystal at 80% RH, 30 °C

| Time, min | W _{hydrate} , % | W _{cocrystal} , % | Rwp |
|-----------|--------------------------|----------------------------|-------|
| 1.4 | 11.7 | 88.3 | 10.12 |
| 4.0 | 38.5 | 61.5 | 10.01 |
| 6.7 | 55.6 | 44.4 | 11.53 |
| 9.3 | 65.7 | 34.3 | 12.50 |
| 12.0 | 71.5 | 28.5 | 13.02 |
| 14.6 | 76.5 | 23.5 | 13.26 |
| 17.3 | 78.7 | 21.3 | 13.54 |
| 20.0 | 81.2 | 18.9 | 13.61 |
| 22.6 | 82.5 | 17.5 | 13.63 |
| 25.3 | 84.9 | 15.1 | 13.83 |
| 28.0 | 85.4 | 14.6 | 13.95 |
| 30.6 | 86.2 | 13.8 | 13.83 |
| 33.3 | 88.0 | 12.0 | 14.01 |
| 36.0 | 88.3 | 11.7 | 14.18 |
| 38.6 | 89.0 | 11.1 | 14.26 |
| 41.3 | 89.7 | 10.3 | 14.11 |
| 44.0 | 89.7 | 10.3 | 14.26 |
| 46.6 | 90.3 | 9.7 | 14.17 |
| 49.3 | 90.8 | 9.2 | 14.09 |
| 52.0 | 91.1 | 8.9 | 14.41 |
| 54.6 | 91.6 | 8.4 | 14.41 |
| 57.3 | 92.0 | 8.0 | 14.21 |

Table S8 Rietveld analysis of kinetic data for the formation of 4-aminosalicylic acid–nicotinamide cocrystal hydrate from starting components at 70% RH, 30 °C

| Time, min | W _{hydrate} , % | W _{4-ASA} , % | W _{nicotinamide} , % | Rwp |
|-----------|--------------------------|------------------------|-------------------------------|-------|
| 1.3 | 0.6 | 51.3 | 48.1 | 10.88 |
| 5.0 | 1.0 | 51.0 | 48.0 | 10.57 |
| 7.6 | 1.0 | 51.2 | 47.9 | 10.34 |
| 10.3 | 2.3 | 51.4 | 46.4 | 10.32 |
| 12.9 | 2.8 | 50.9 | 46.3 | 10.36 |
| 15.6 | 3.9 | 50.3 | 45.8 | 9.85 |
| 18.3 | 4.9 | 49.9 | 45.2 | 10.00 |
| 20.9 | 5.3 | 49.6 | 45.1 | 10.06 |
| 23.6 | 6.2 | 49.1 | 44.7 | 10.07 |
| 26.3 | 6.2 | 49.5 | 44.3 | 10.17 |
| 28.9 | 6.9 | 48.8 | 44.3 | 10.03 |
| 31.6 | 7.6 | 48.5 | 43.9 | 9.80 |
| 34.2 | 8.0 | 48.4 | 43.7 | 10.00 |
| 36.9 | 8.1 | 48.0 | 43.8 | 9.96 |
| 39.5 | 8.5 | 48.3 | 43.3 | 10.11 |
| 42.2 | 9.3 | 48.0 | 42.7 | 9.79 |
| 44.9 | 9.1 | 48.0 | 43.0 | 9.94 |
| 47.5 | 9.5 | 47.6 | 42.9 | 9.95 |
| 50.2 | 9.8 | 47.4 | 42.7 | 9.76 |
| 52.8 | 10.3 | 47.2 | 42.6 | 9.84 |
| 55.5 | 10.0 | 47.7 | 42.3 | 9.92 |
| 58.1 | 10.5 | 47.6 | 42.0 | 9.69 |
| 60.8 | 11.1 | 46.7 | 42.2 | 9.94 |
| 63.4 | 10.9 | 46.8 | 42.3 | 9.74 |
| 66.1 | 11.5 | 46.4 | 42.1 | 9.72 |
| 68.8 | 11.6 | 46.4 | 42.0 | 9.74 |
| 71.4 | 11.6 | 46.5 | 41.9 | 9.56 |
| 74.1 | 11.8 | 46.3 | 41.9 | 9.84 |
| 76.7 | 12.3 | 46.2 | 41.5 | 9.87 |
| 79.4 | 12.7 | 45.9 | 41.5 | 9.71 |
| 82.1 | 12.8 | 45.8 | 41.4 | 9.84 |
| 84.7 | 12.4 | 46.2 | 41.3 | 9.79 |
| 87.4 | 13.2 | 45.4 | 41.4 | 9.75 |
| 90.0 | 13.6 | 45.3 | 41.1 | 10.02 |
| 98.0 | 13.4 | 45.7 | 40.8 | 9.77 |

Table S9 Rietveld analysis of kinetic data for the formation of 4-aminosalicylic acid–nicotinamide cocrystal hydrate from starting components at 80% RH, 30 °C

| Time, min | W _{hydrate} , % | W _{4-ASA} , % | W _{nicotinamide} , % | Rwp |
|-----------|--------------------------|------------------------|-------------------------------|------|
| 1.3 | 4.1 | 51.2 | 44.8 | 8.85 |
| 4.0 | 7.1 | 49.5 | 43.4 | 8.91 |
| 6.7 | 9.1 | 48.3 | 42.6 | 8.81 |
| 9.3 | 10.8 | 47.2 | 42.0 | 8.83 |
| 12.0 | 12.4 | 47.0 | 40.6 | 8.82 |
| 14.7 | 13.5 | 46.6 | 39.9 | 9.07 |
| 17.3 | 14.6 | 45.8 | 39.6 | 8.97 |
| 22.7 | 16.6 | 44.7 | 38.6 | 8.65 |
| 25.3 | 17.4 | 44.2 | 38.3 | 8.96 |
| 30.7 | 18.3 | 43.5 | 38.2 | 8.57 |
| 33.3 | 19.7 | 43.1 | 37.2 | 8.87 |
| 38.7 | 20.2 | 42.6 | 37.2 | 8.84 |
| 44.0 | 21.5 | 42.2 | 36.4 | 8.77 |
| 49.4 | 22.1 | 41.9 | 36.1 | 8.98 |
| 57.4 | 23.7 | 40.8 | 35.5 | 8.83 |
| 65.4 | 25.0 | 40.2 | 34.8 | 8.81 |
| 70.7 | 25.6 | 39.7 | 34.8 | 8.85 |
| 81.4 | 26.7 | 39.5 | 33.8 | 8.77 |
| 94.8 | 27.6 | 39.3 | 33.1 | 8.79 |

Table S10 Rietveld analysis of kinetic data for the formation of 4-aminosalicylic acid–nicotinamide cocrystal hydrate from starting components at 90% RH, 30 °C

| Time, min | W _{hydrate} , % | W _{4-ASA} , % | W _{nicotinamide} , % | Rwp |
|-----------|--------------------------|------------------------|-------------------------------|-------|
| 1.3 | 23.9 | 44.5 | 31.6 | 10.02 |
| 4.0 | 37.9 | 35.5 | 26.6 | 8.67 |
| 6.6 | 41.1 | 33.5 | 25.4 | 8.94 |
| 9.3 | 43.6 | 32.1 | 24.3 | 9.17 |
| 12.0 | 44.9 | 31.5 | 23.6 | 9.12 |
| 14.6 | 46.5 | 30.5 | 23.0 | 9.06 |
| 17.3 | 47.5 | 29.7 | 22.8 | 8.97 |
| 19.9 | 48.6 | 29.3 | 22.2 | 9.03 |
| 22.6 | 49.4 | 28.7 | 21.9 | 9.06 |
| 27.9 | 50.5 | 28.1 | 21.4 | 9.45 |
| 33.3 | 51.5 | 27.3 | 21.2 | 9.10 |
| 38.6 | 52.9 | 26.4 | 20.7 | 9.40 |
| 43.9 | 53.5 | 26.2 | 20.3 | 8.94 |
| 46.5 | 53.7 | 26.0 | 20.3 | 9.32 |
| 59.8 | 55.0 | 25.5 | 19.5 | 9.33 |
| 73.1 | 56.0 | 24.8 | 19.2 | 9.14 |
| 83.8 | 56.9 | 24.3 | 18.8 | 9.26 |
| 97.1 | 58.0 | 24.0 | 18.1 | 9.35 |

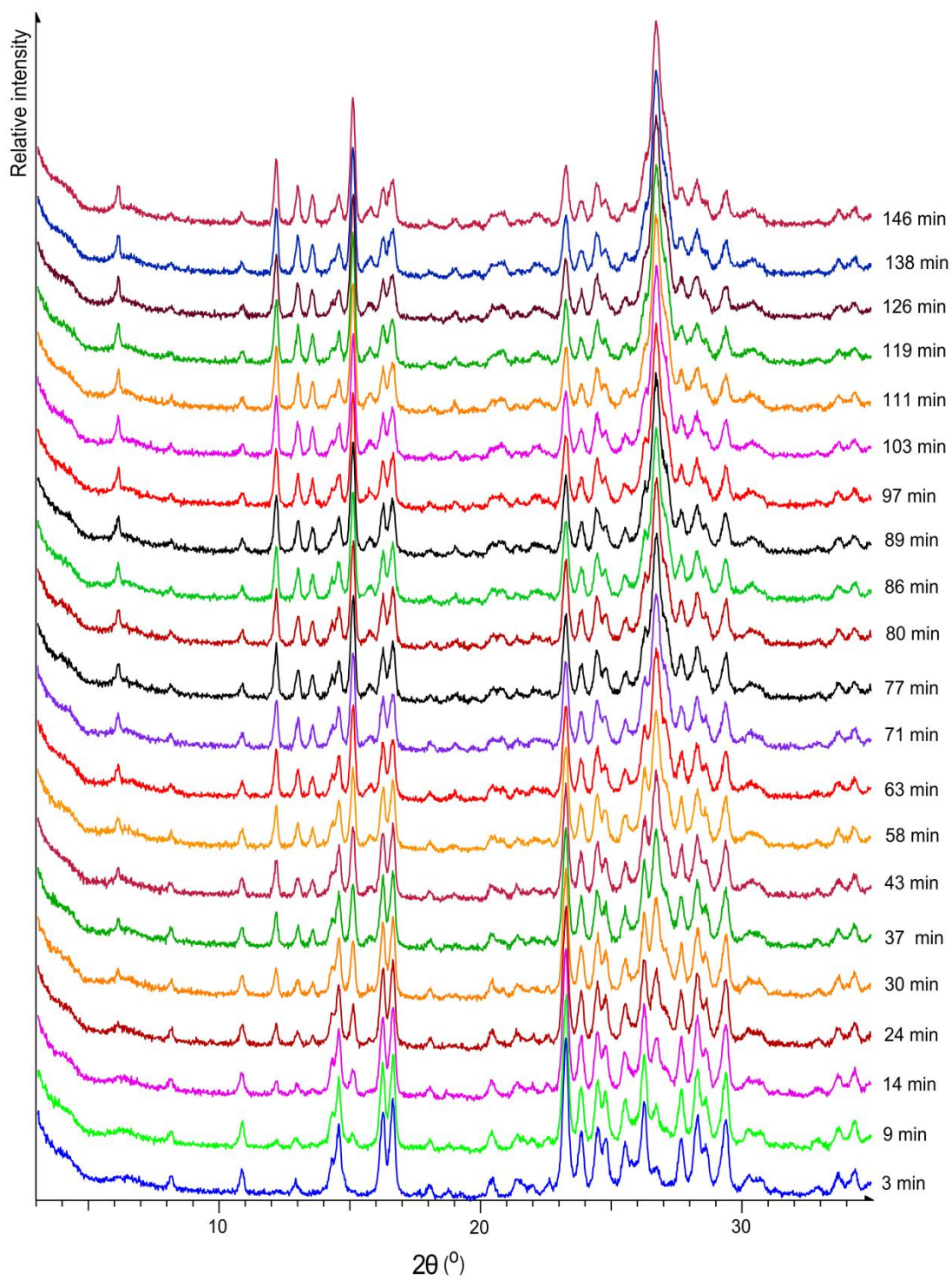


Fig. S1 Diffraction patterns for the hydration of anhydrous 4-aminosalicylic acid–nicotinamide cocrystal at 40% RH, 30 °C

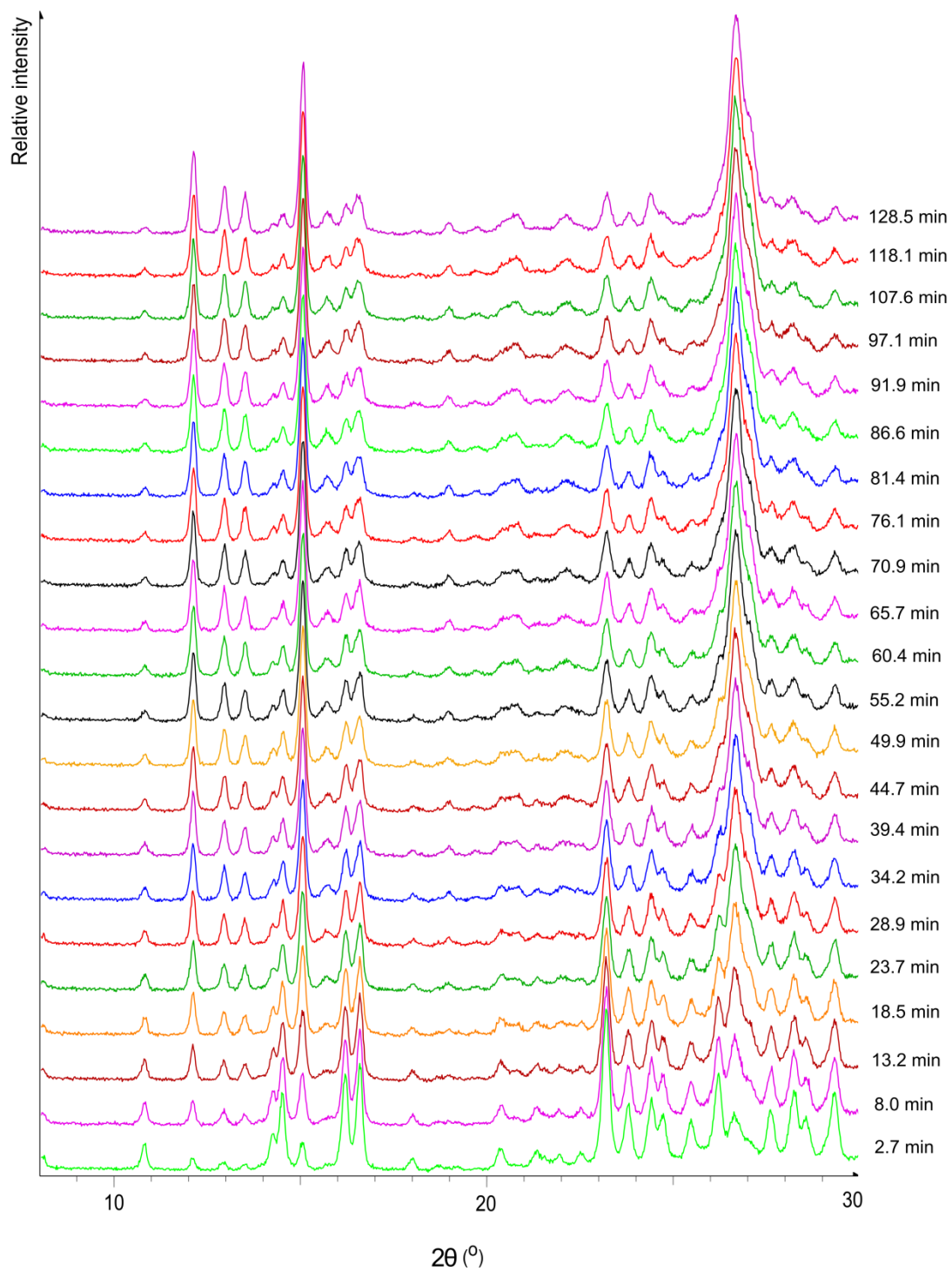


Fig. S2 Diffraction patterns for the hydration of anhydrous 4-aminosalicylic acid–nicotinamide cocrystal at 50% RH, 30 °C

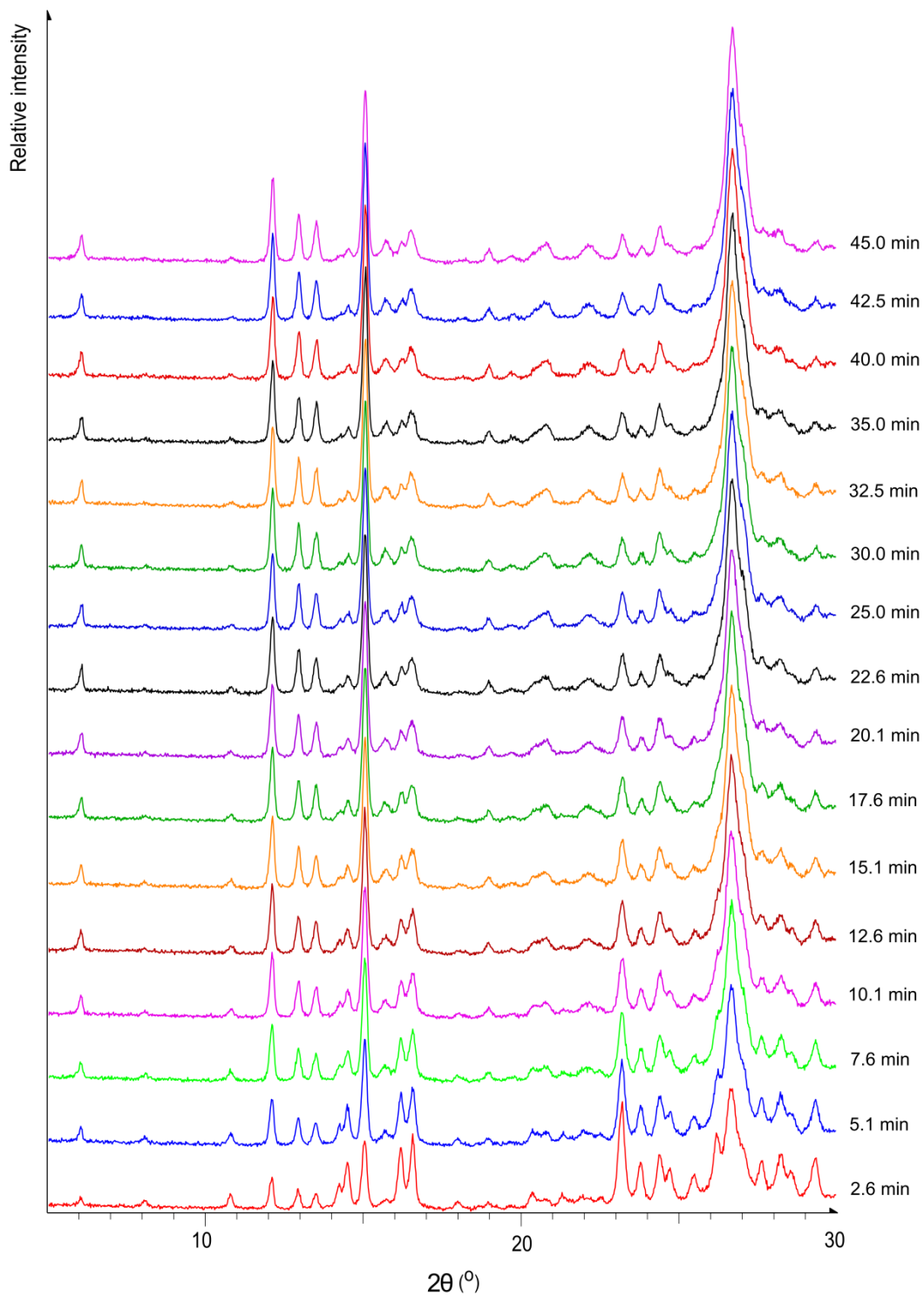


Fig. S3 Diffraction patterns for the hydration of anhydrous 4-aminosalicylic acid-nicotinamide cocrystal at 70% RH, 30 °C

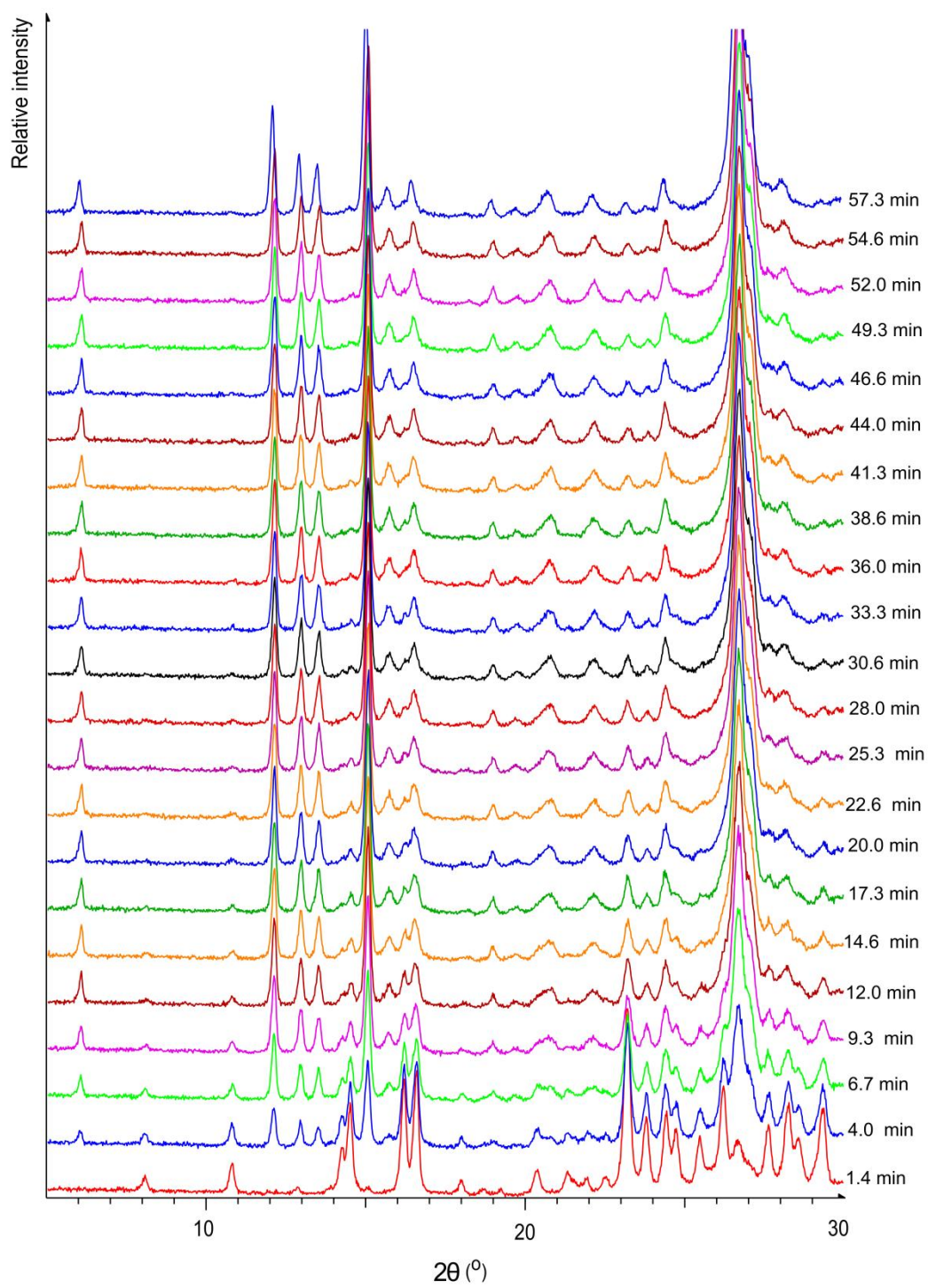


Fig. S4 Diffraction patterns for the hydration of anhydrous 4-aminosalicylic acid–nicotinamide cocrystal at 80% RH, 30 °C

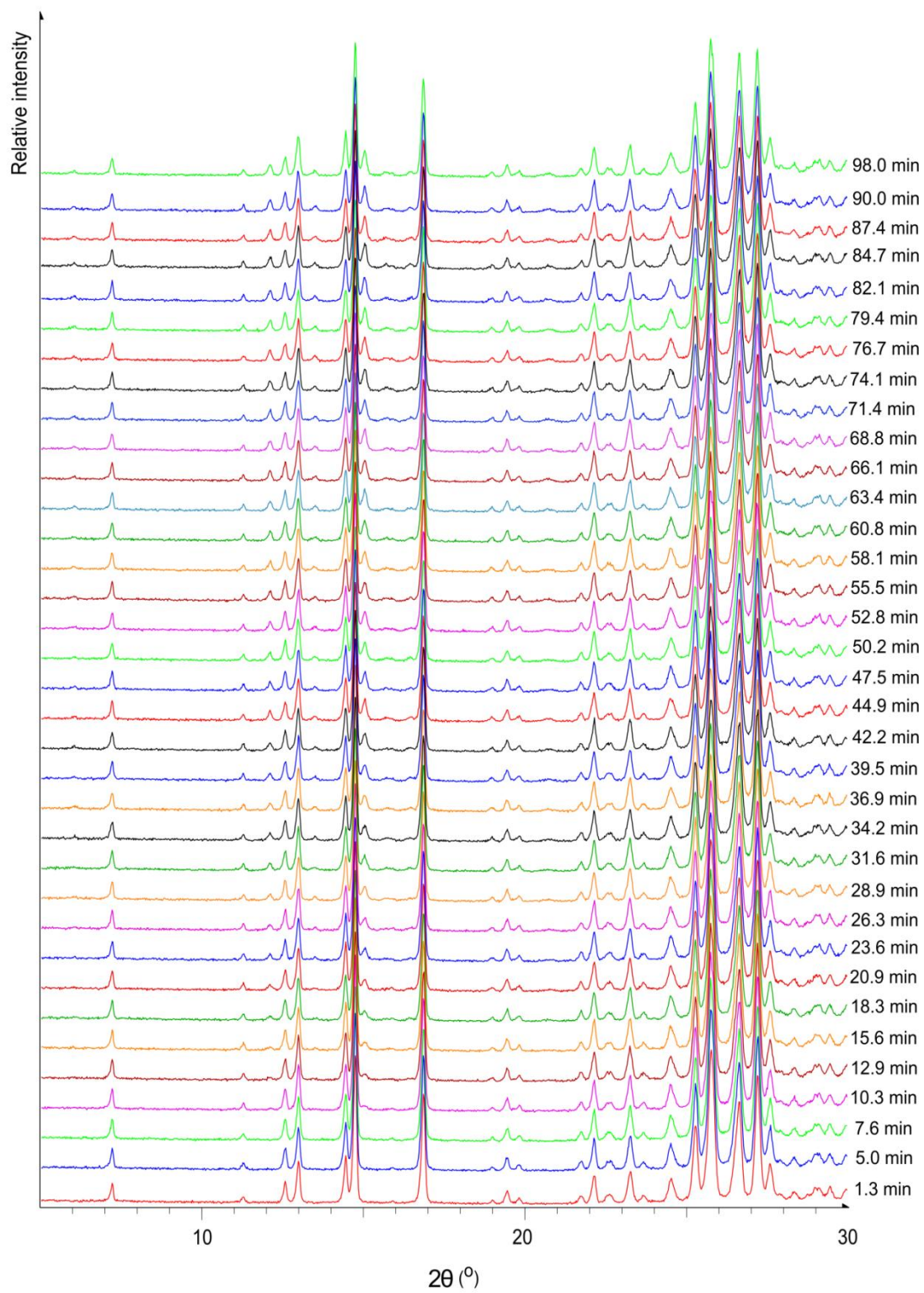


Fig. S5 Diffraction patterns for the formation of 4-aminosalicylic acid–nicotinamide cocrystal monohydrate at 70% RH, 30 °C from starting compounds

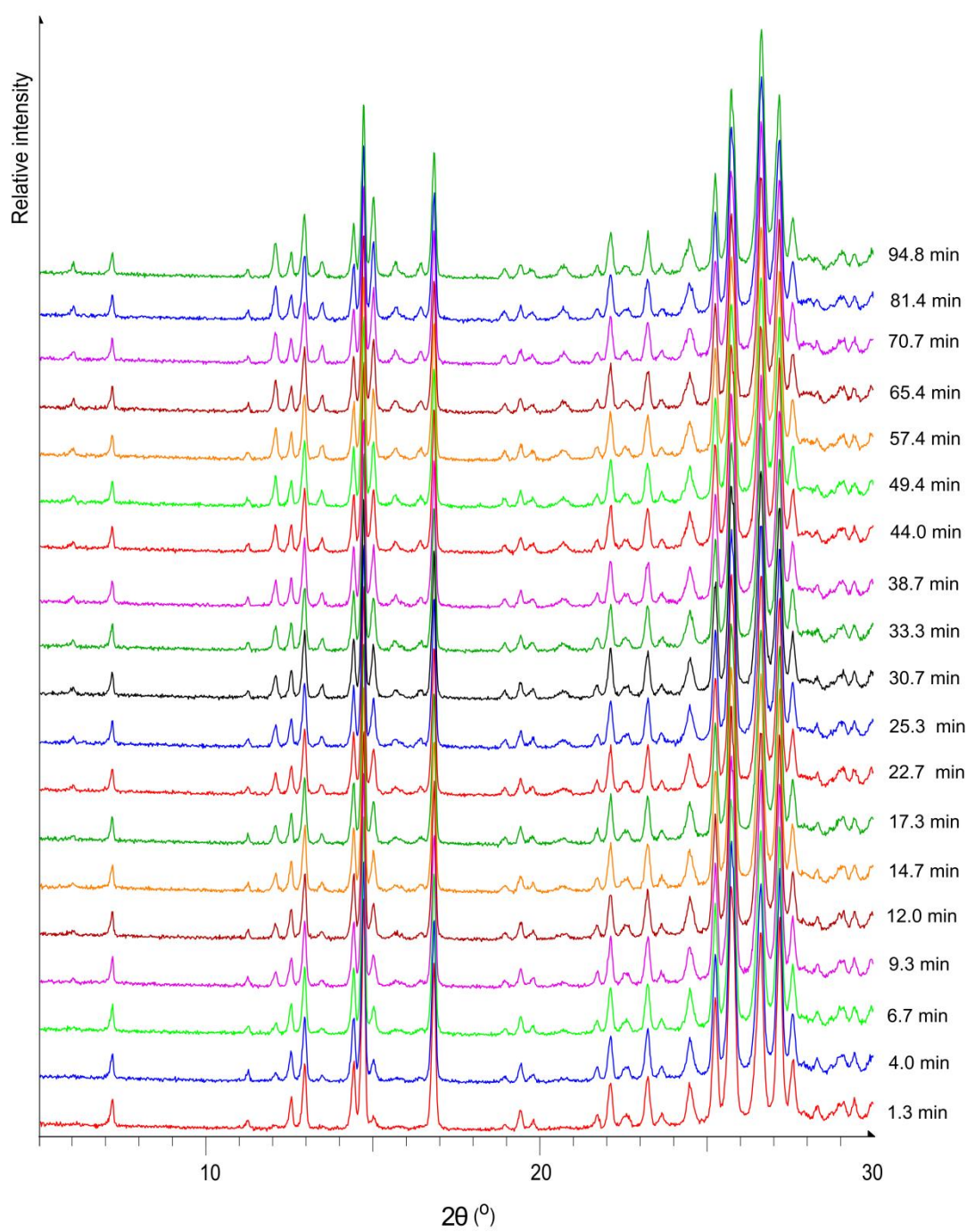


Fig. S6 Diffraction patterns for the formation of 4-aminosalicylic acid–nicotinamide cocrystal monohydrate at 80% RH, 30 °C from starting compounds

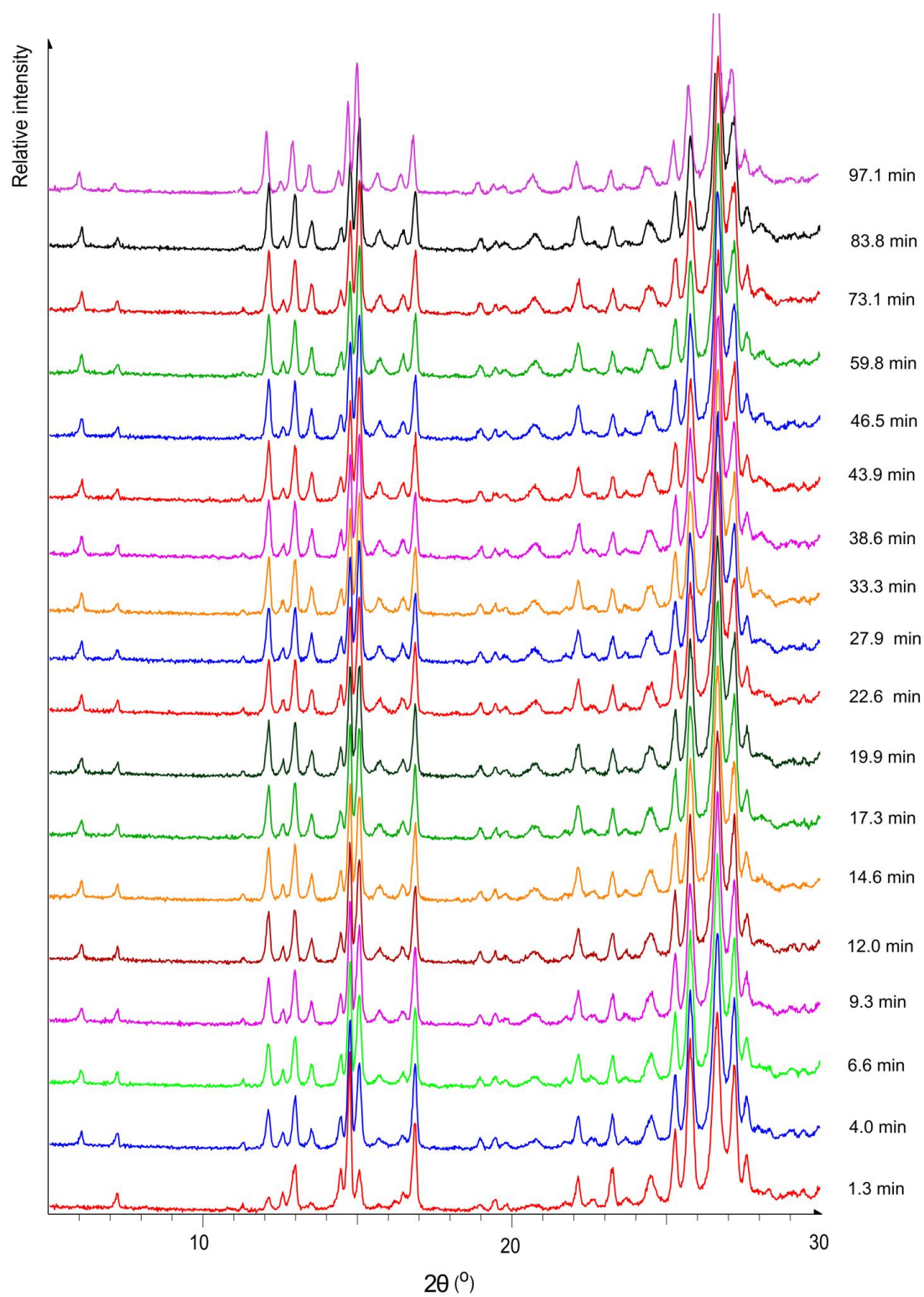


Fig. S7 Diffraction patterns for the formation of 4-aminosalicylic acid–nicotinamide cocrystal monohydrate at 90% RH, 30 °C from starting compounds