Mechanochemistry for the production of a hybrid salt used in the treatment of malaria

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Supporting Information

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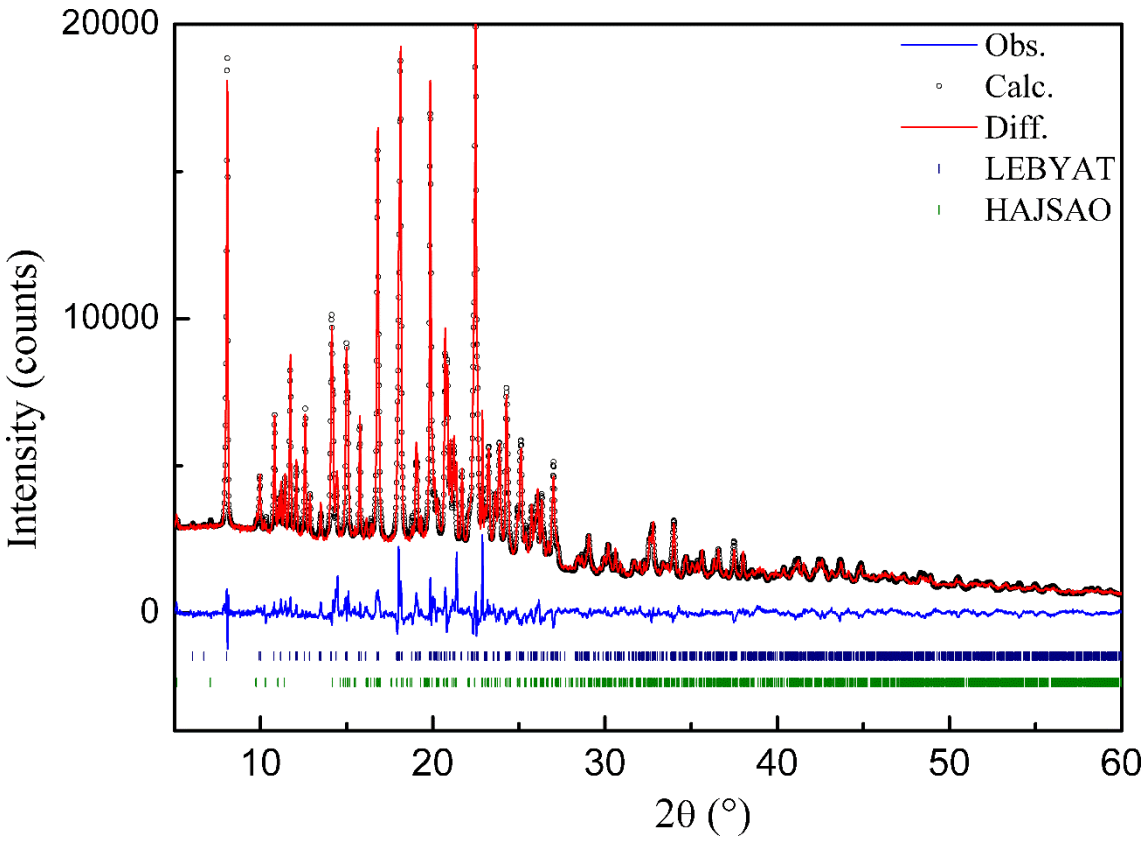

Figure S1. Plot from the final Rietveld refinement of mefloquine containing the phases used for quantitative phase analysis: mefloquine base (CSD code: LEBYAT[1]) and mefloquine hydrochloride (CSD code: HAJSAO[2]). Black circles represent observed data, the red solid line indicates the calculated profile and their difference (blue line) is shown at the bottom. Tick marks (vertical bars) at the bottom of the pattern indicate peak positions allowed by the unit cell parameters and space groups of phases LEBYAT and HAJSAO.

Table S1. Crystal data and details of the structure refinement for mefloquine. The letters *a, b* and *c* indicate the lengths of the unit cell (Å); *α, β* and *γ* display the unit cell angles (°); R_{wp}, R_{exp}, R_{Bragg} and χ^2 represent the statistical indices describing the final Rietveld refinement, demonstrating that a satisfying fit was obtained.

Crystal data and structure refinement details (mefloquine)	
Mefloquine phase	
a, b, c (Å)	17.908(1), 8.835(1), 22.117(1)
α, β, γ (°)	90, 95.978(3), 90
Mefloquine Hydrochloride phase	
a, b, c (Å)	6.085(1), 17.389(2), 18.277(3)
α, β, γ (°)	89.010(9), 83.310(9), 81.350(9)
R_{wp} (%)	5.76
R_{exp} (%)	2.09
R_{Bragg} (%)	2.87 (Mefloquine) 3.89 (Mefloquine Hydrochloride)
χ^2	2.75

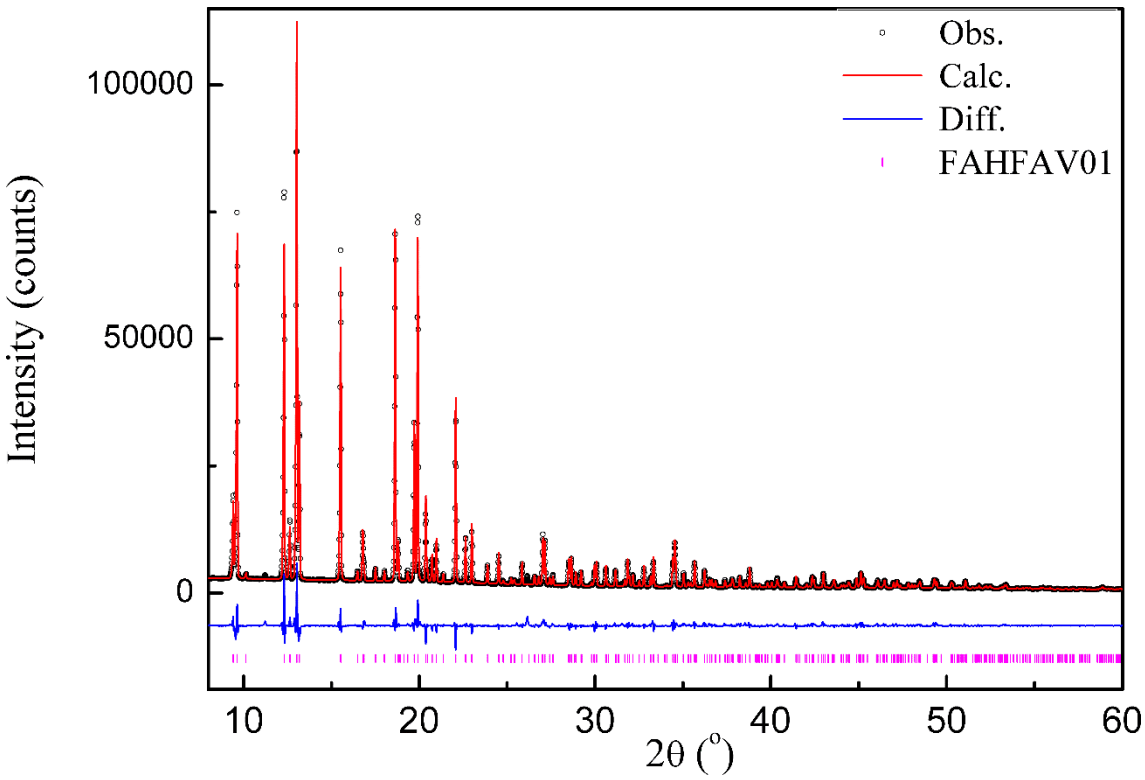

Figure S2. Plot from the final Rietveld refinement of artesunate (CSD code: FAHFAV01[3]). Black circles represent observed data, the solid red line is the calculated profile and their difference (blue line) is shown at the bottom. Tick marks (vertical bars) at the bottom of the pattern indicate peak positions allowed by the unit cell parameters and space group FAHFAV01.

Table S2. Crystal data and details of the structure refinement for artesunate. The letters *a, b* and *c* indicate the lengths of the unit cell (Å); *α, β* and *γ* display the unit cell angles (°); R_{wp}, R_{exp}, R_{Bragg} and χ^2 represent the statistical indices describing the final Rietveld refinement, demonstrating that a satisfying fit was obtained.

Crystal data and structure refinement details (artesunate)	
Artesunate phase	
a, b, c (Å)	9.835(1),10.510(3),18.752(3)
α, β, γ (°)	90, 90, 90
R_{wp} (%)	6.29
R_{exp} (%)	1.89
R_{Bragg} (%)	3.63
χ^2	3.32

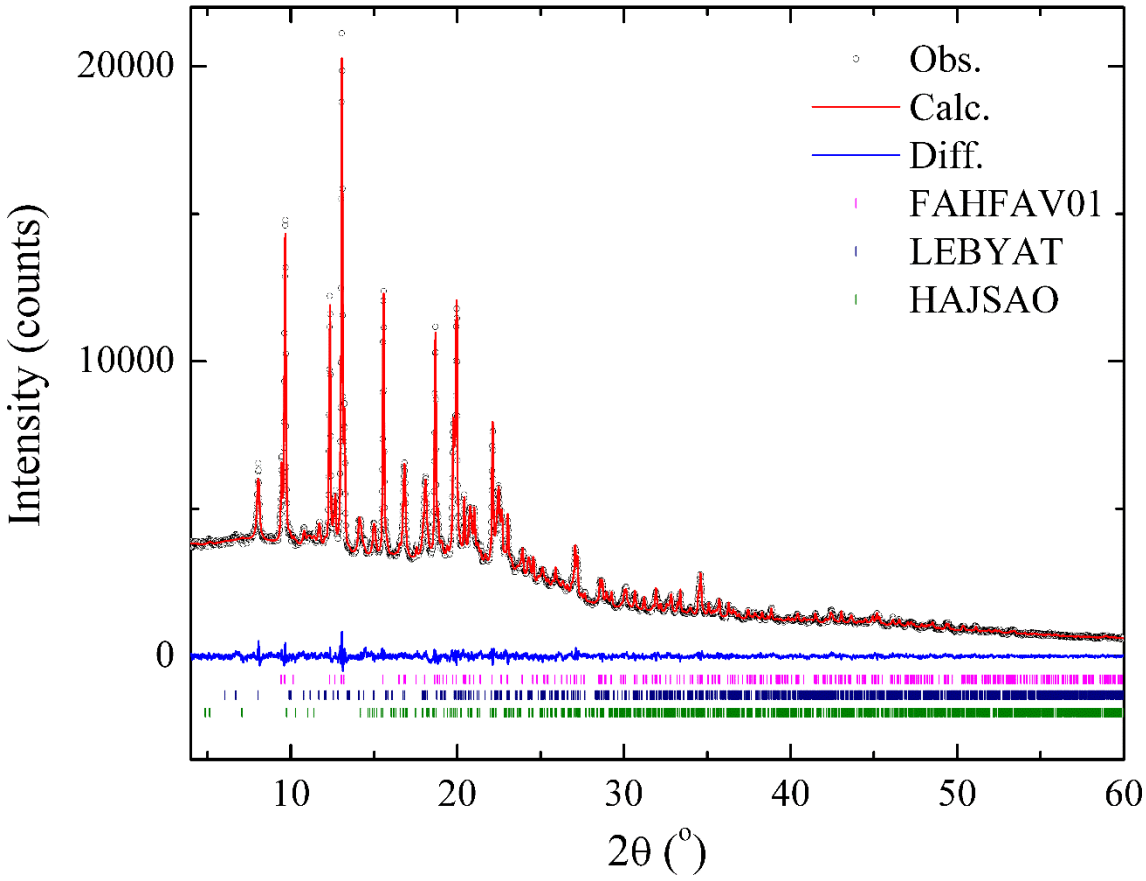

Figure S3. Plot from the final Rietveld refinement of sample η = 0 μL·mg^{-1} containing the phases: artesunate (CSD code: FAHFAV01[21]), mefloquine base (CSD code: LEBYAT[22]), mefloquine hydrochloride (CSD code: HAJSAO[23]). Black circles represent observed data, the solid red line is the calculated profile and their difference (blue line) is shown at the bottom. Tick marks (vertical bars) at the bottom of the pattern indicate peak positions allowed by the unit cell parameters and space groups of phases FAHFAV01, LEBYAT and HAJSAO.

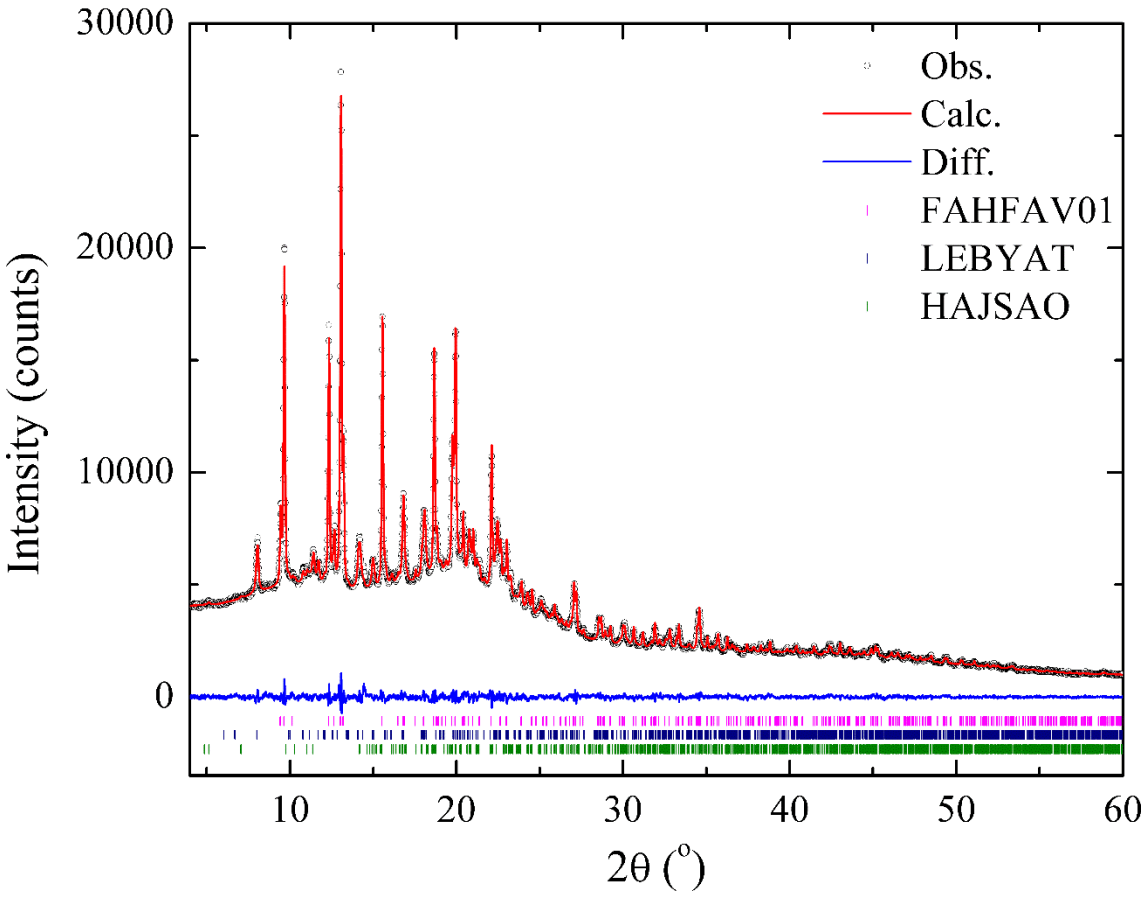

Figure S4. Plot from the final Rietveld refinement of sample η = 0.1 μL·mg^{-1} containing the phases: artesunate (CSD code: FAHFAV01[21]), mefloquine base (CSD code: LEBYAT[22]), mefloquine hydrochloride (CSD code: HAJSAO[23]). Black circles represent observed data, the solid red line is the calculated profile and their difference (blue line) is shown at the bottom. Tick marks (vertical bars) at the bottom of the pattern indicate peak positions allowed by the unit cell parameters and space groups of phases FAHFAV01, LEBYAT and HAJSAO.

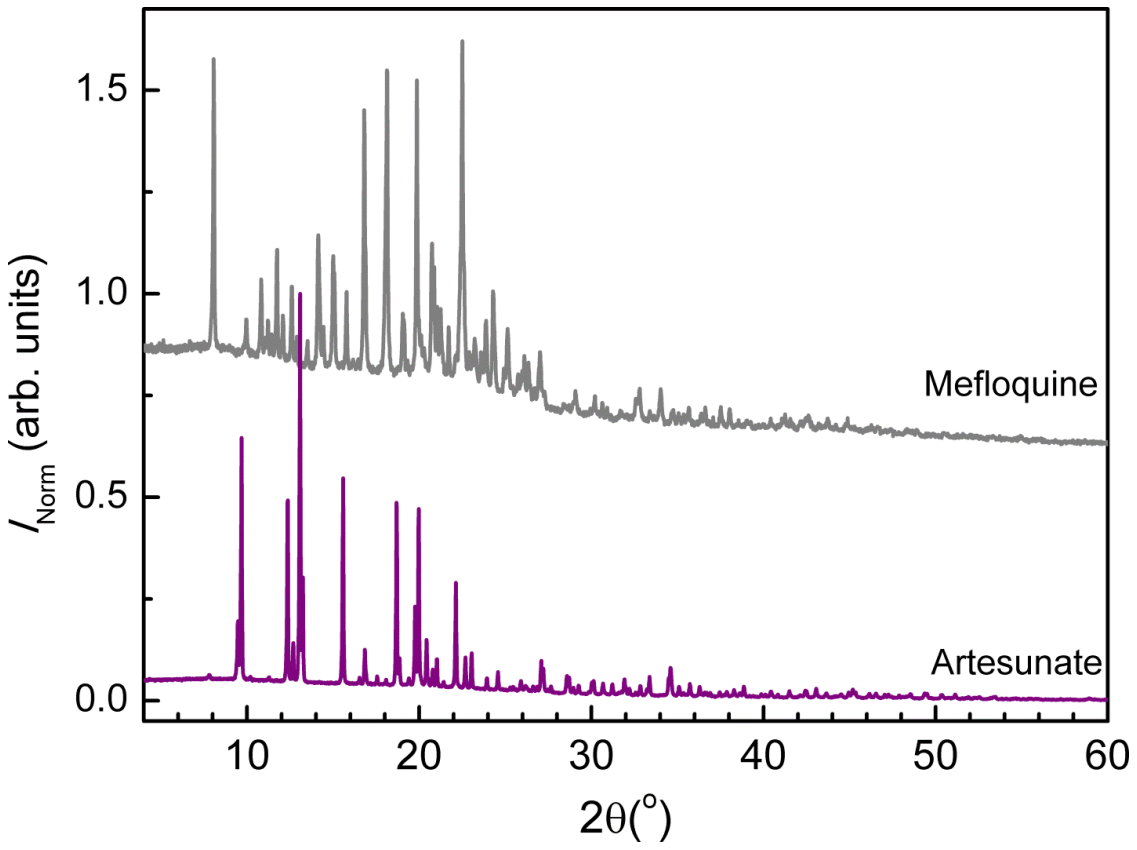

Figure S5. Normalized powder X-ray diffraction patterns of mefloquine and artesunate after 15 minutes of liquid-assisted grinding. The curves were vertically shifted for better visualization.

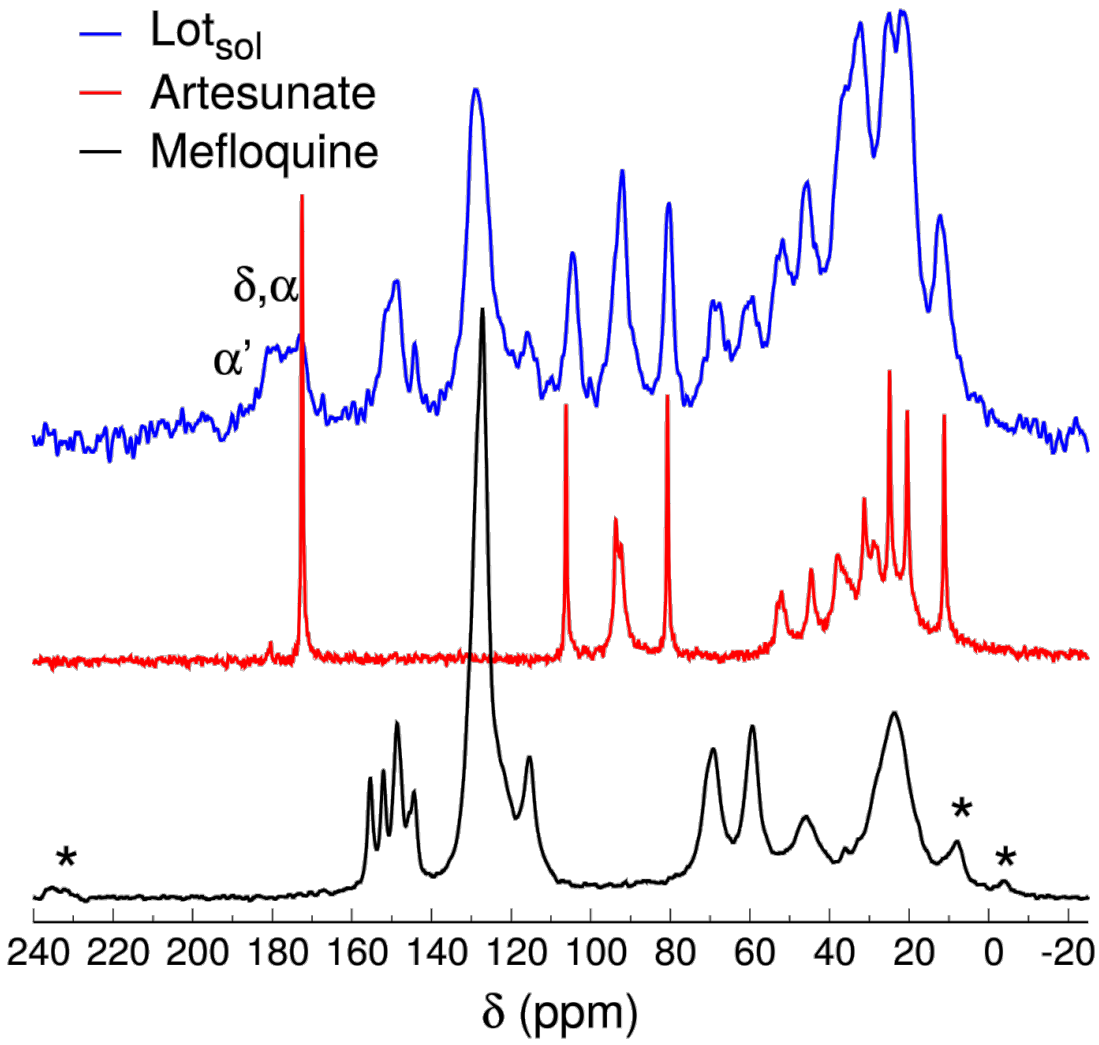

Figure S6. $^{13}C\{^{1}H\}$ CP-MAS spectra of Mefloquine, Artesunate, and MEFAS$_{sol}$ (solution-phase synthesis). Asterisks indicate spinning sidebands.

Milling Time

We also evaluate the effect of the milling time. Figure S7- S10 show the ATR-FTIR spectra of mefloquine base, artesunate, MEFAS $Lot_{solution}$, dihydroartemisinin (DHA) and milling time experiments from different η (η = 1 μL mg^{-1}, η = 0.5 μL mg^{-1}, η = 0.1 μL mg^{-1} and η = 0 μL mg^{-1}). The milling time did not influence the reactivity of the mechanochemical syntheses as the amount of the solvent.

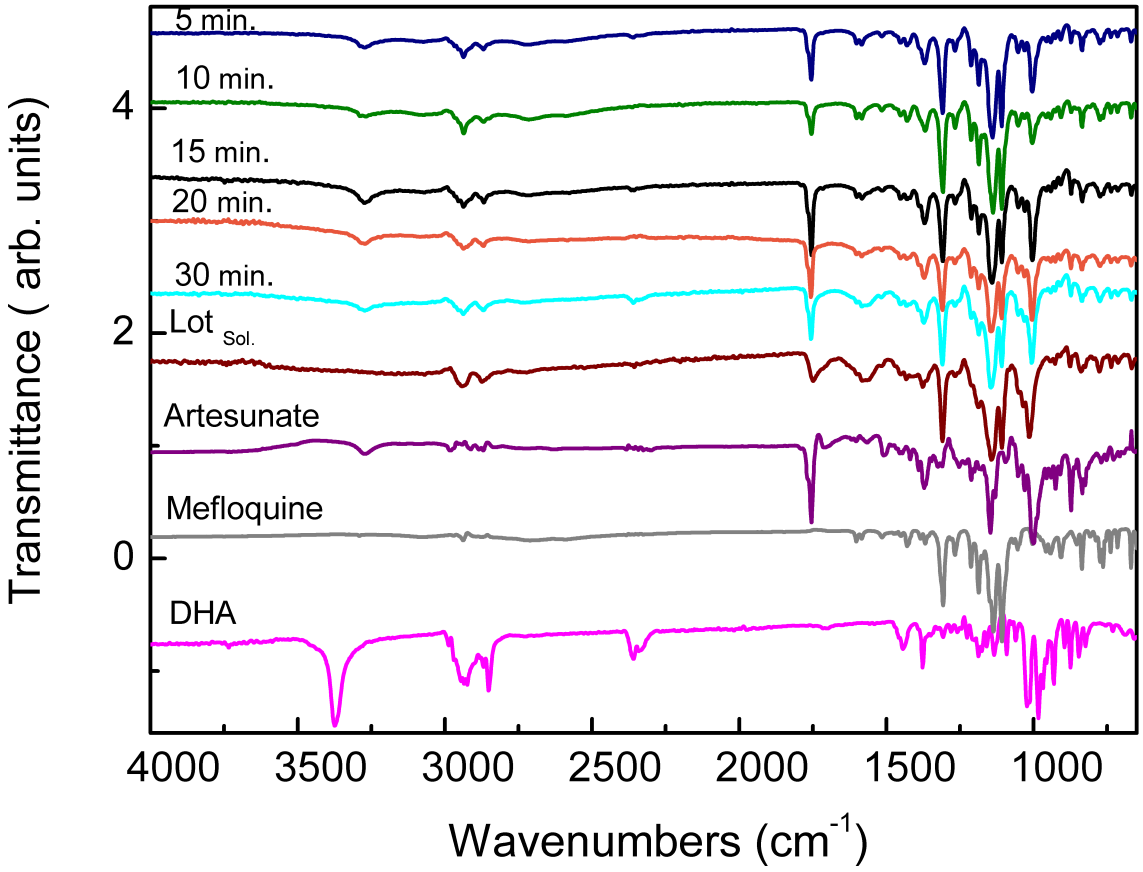

Figure S7. ATR-FTIR spectra of milling time experiments (η = 0 μL·mg^{-1}), MEFAS $Lot_{solution}$ (Lot_{sol}), Artesunate, Mefloquine and dihydroartemisinin (DHA).

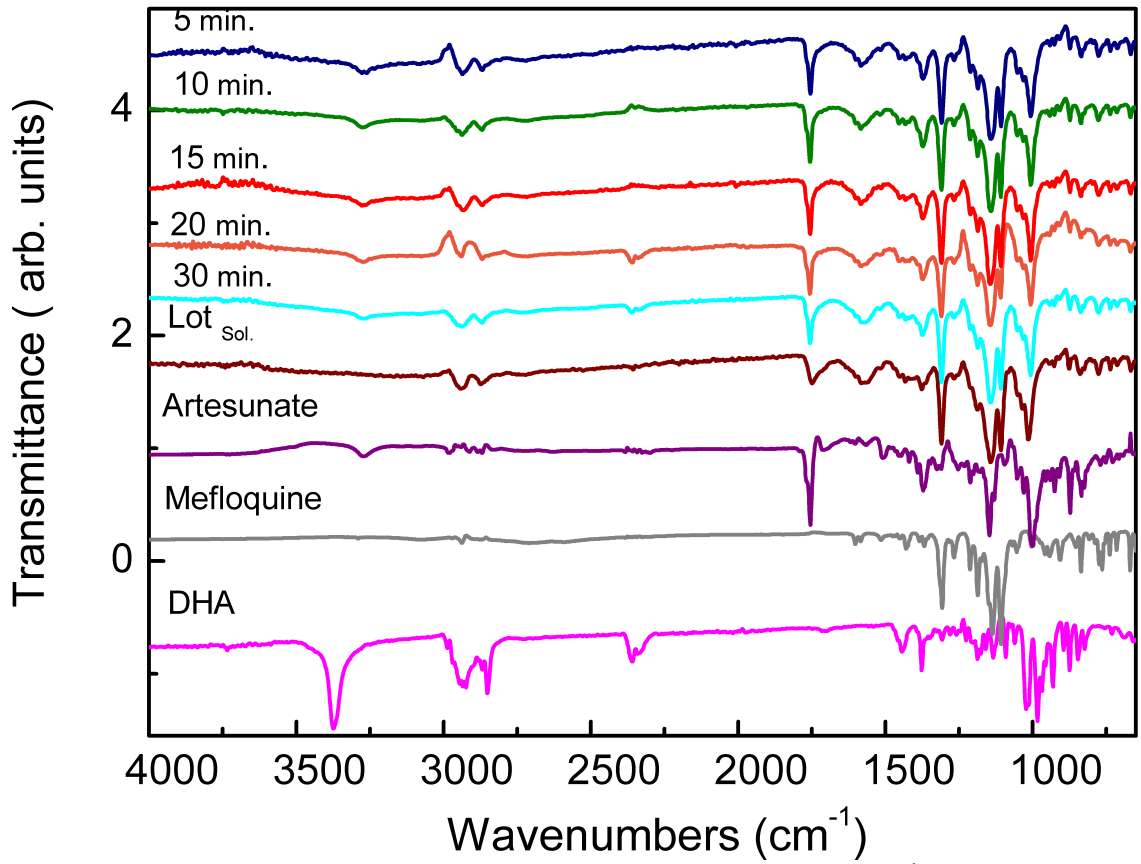

Figure S8. ATR-FTIR spectra of milling time experiments (η = 0.1 µL·mg^{-1}), MEFAS Lot$_{solution}$ (Lot$_{sol}$), Artesunate, Mefloquine and dihydroartemisinin (DHA).

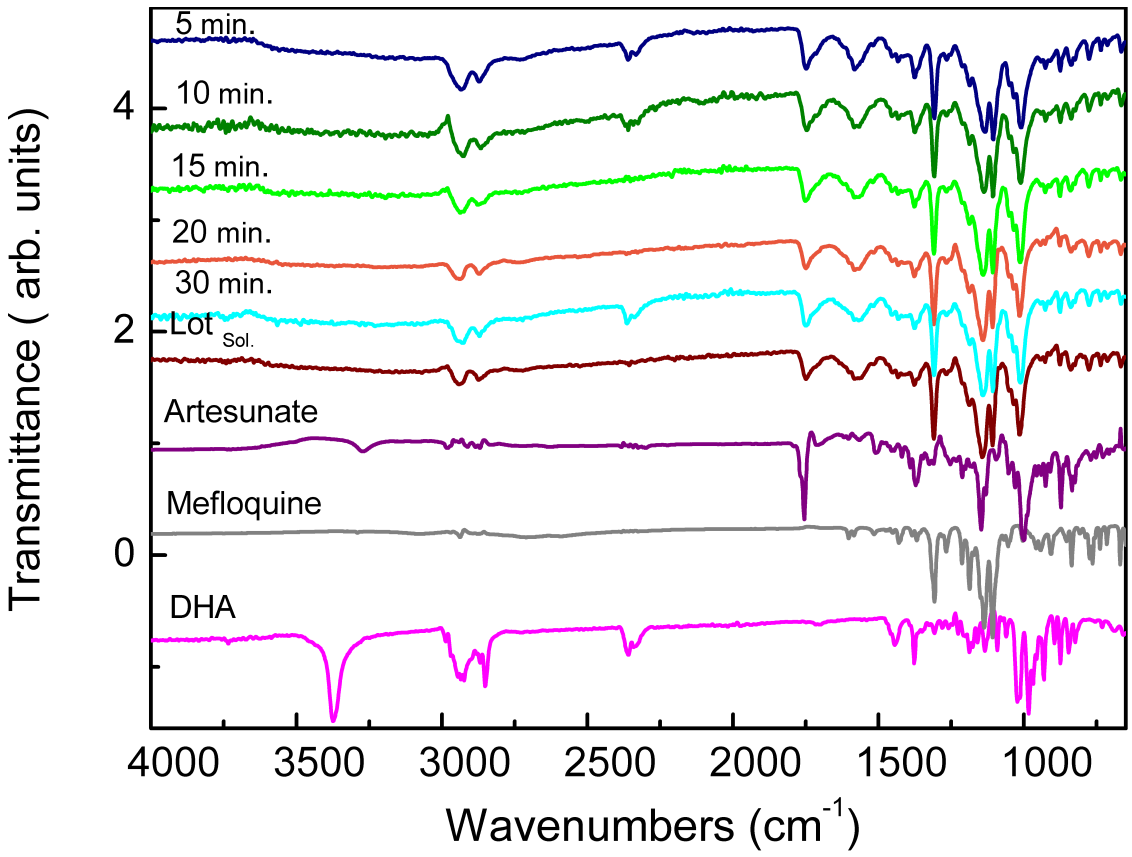

Figure S9. ATR-FTIR spectra of milling time experiments (η = 0.5 μL·mg^{-1}), MEFAS Lot$_{solution}$ (Lot$_{sol}$), Artesunate, Mefloquine and dihydroartemisinin (DHA).

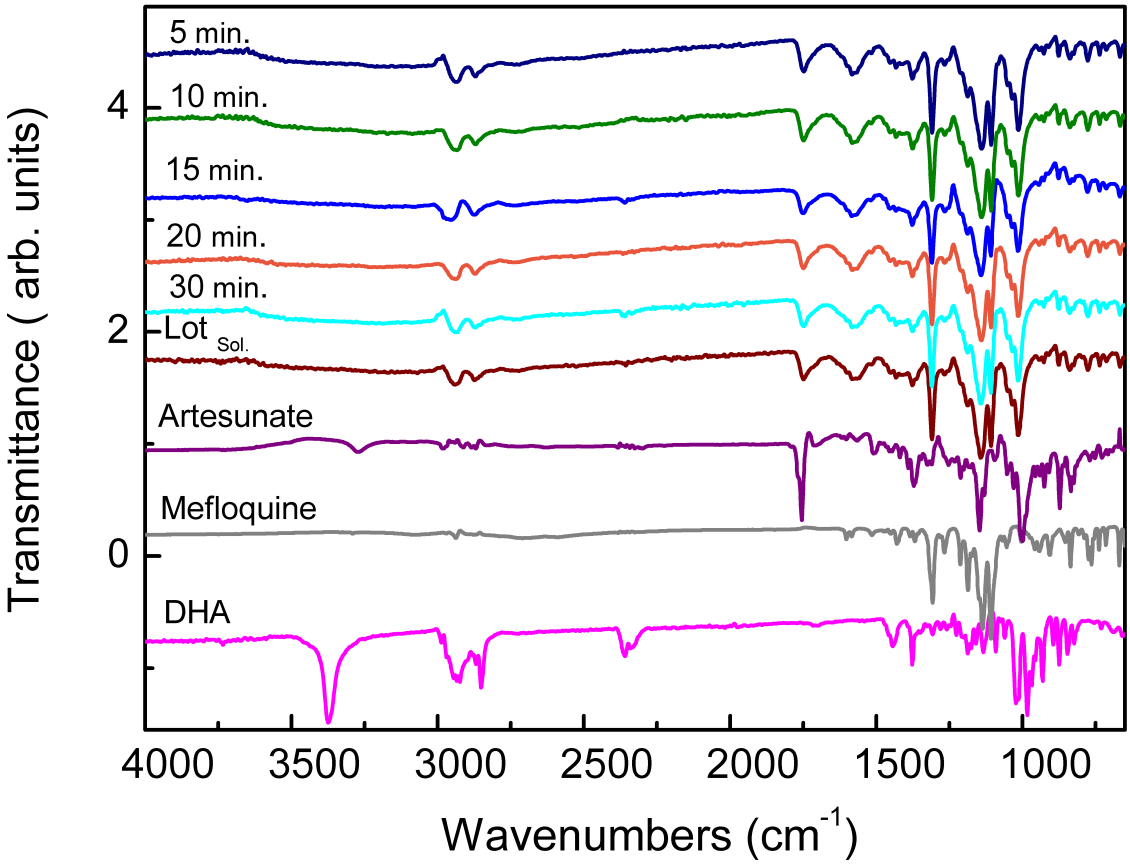

Figure S10. ATR-FTIR spectra of milling time experiments (η = 1 µL·mg^{-1}), MEFAS Lot$_{solution}$ (Lot$_{sol}$), Artesunate, Mefloquine and dihydroartemisinin (DHA).

The powder X-ray diffraction patterns of the milling time experiments from different η are shown in Figure S11 – S14. For η = 0 μL·mg^{-1} and η = 0.1 μL·mg^{-1} there is no clear influence of the milling time on the degree of crystallinity. For η = 0.5 μL·mg^{-1} and η = 1 μL·mg^{-1} the milling time greatly decreases the degree of crystallinity.

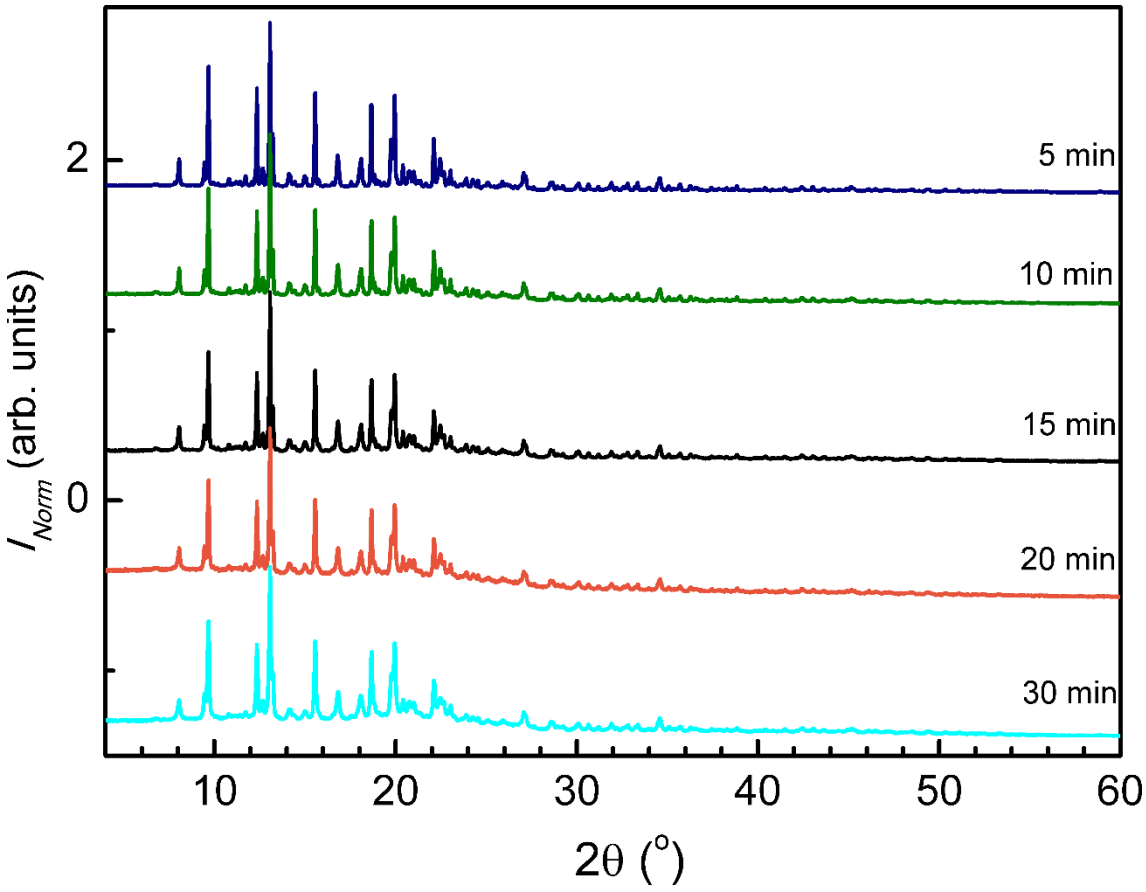

Figure S11. Normalized powder X-ray diffraction patterns time milling experiments (η = 0 μL mg^{-1}).

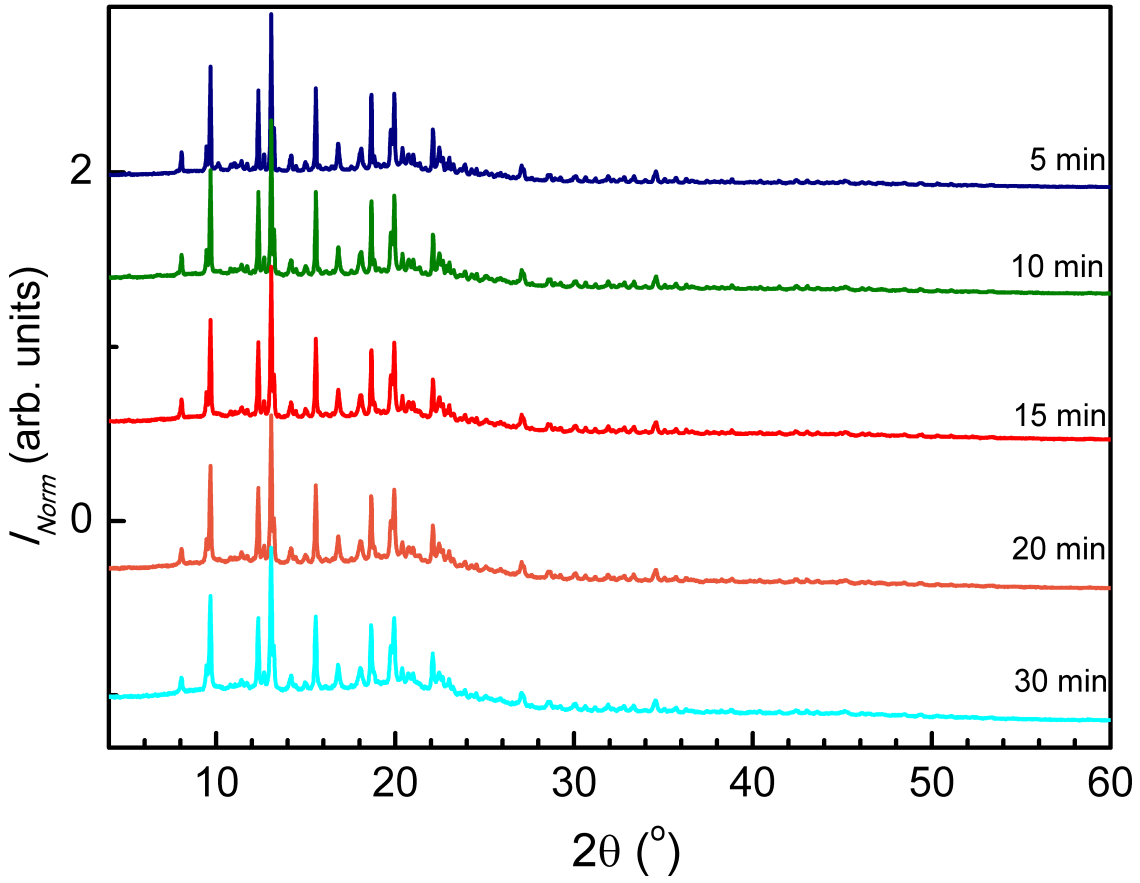

Figure S12. Normalized powder X-ray diffraction patterns time milling experiments (η = 0.1 μL mg^{-1}).

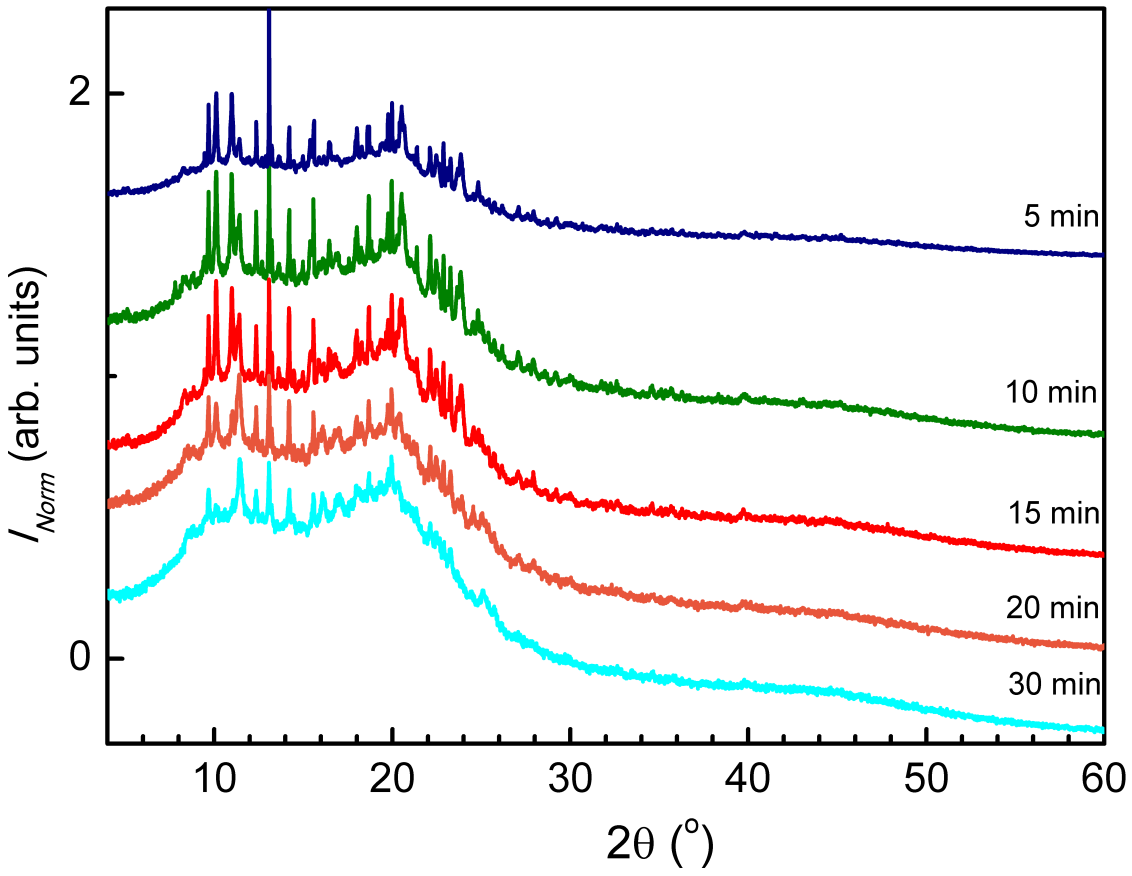

Figure S13. Normalized powder X-ray diffraction patterns time milling experiments (η = 0.5 µL mg^{-1}).

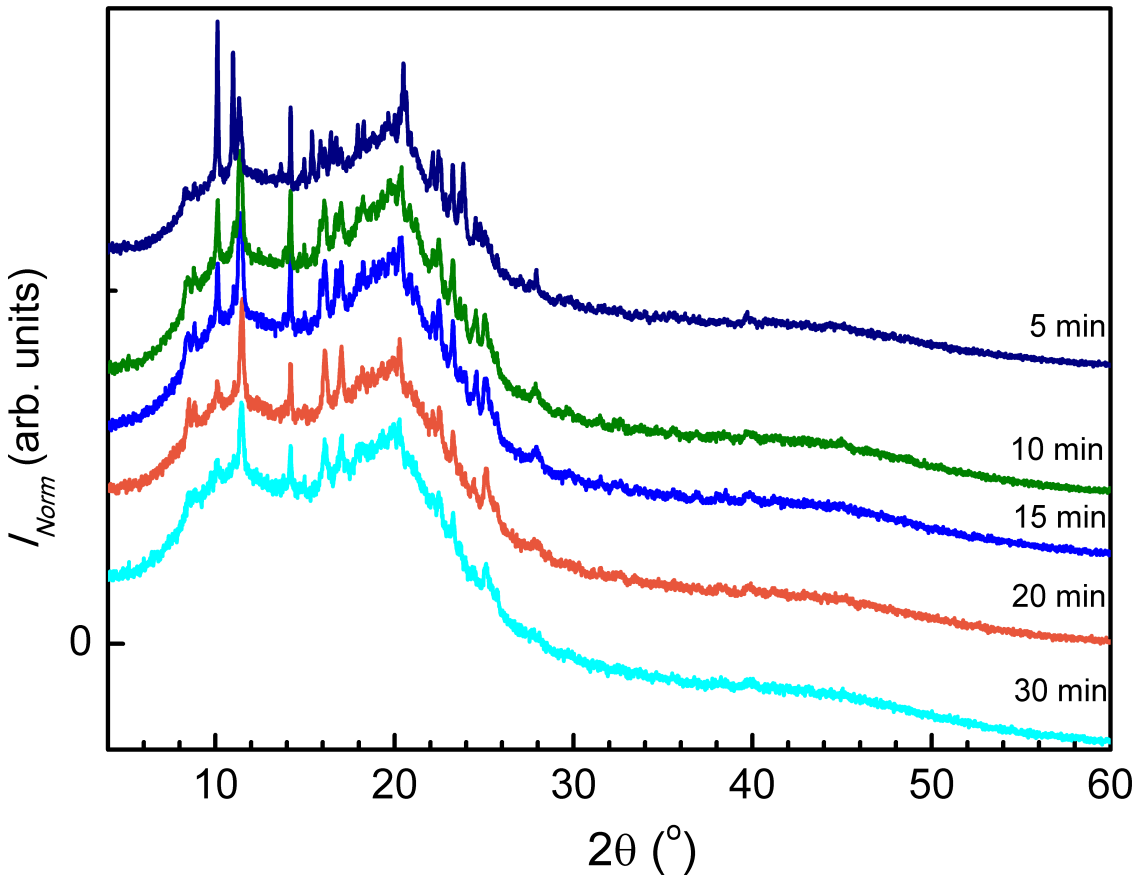

Figure S14. Normalized powder X-ray diffraction patterns time milling experiments (η = 1 μL mg^{-1}).