Electronic Supplementary Information

"Wash-free" synthesis of cyclodextrin metal-organic frameworks

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Experimental

Materials

Potassium hydrogen carbonate ($KHCO_3$, >99.5 %), potassium acetate (CH_3COOK, >97.0 %), potassium hydroxide (KOH, >85.0 %), potassium chloride (KCl, >99.5 %), potassium carbonate (K_2CO_3, >99.5 %), gamma-cyclodextrin (CD, >97.0 %), levofloxacin (>98.0 %), methanol (>99.5 %) and ethanol (>99.5 %) were purchased from Fujifilm Wako Pure Chemical Corporation. All chemicals were used without further purification.

Synthesis

Wash-free mechanochemical synthesis: CD and potassium source ($KHCO_3$, CH_3COOK, KOH, KCl or K_2CO_3) together with a small amount of ethanol were placed in a 250 ml zirconia milling jar containing 30 YTZ® balls. Typically, the molar ratio of mixture is CD : K^+ : ethanol = 1 : 2 : 0.04; the K^+/CD ratio can be varied from 0.67 to 8 and the ethanol/CD ratio can be reduced to 0.0085. These were then milling at a rotation rate of 150 rpm for 5 min by using planetary mill Pulverisette 6 (Fritsch Japan). The products were only dried under atmospheric pressure at 60 °C or 80 °C for 1 h.

Vapor diffusion method: CD-MOF was prepared as described by Smaldone et al.[1] with some minor modifications. 1 mmol of CD and 8 mmol of KOH were dissolved in 20 mL of deionized water. The aqueous solution was filtered with a 0.20-μm nylon membrane. The container containing the aqueous solution was placed in a container containing 50 mL of methanol and exposed to vapor diffusion at 30 °C. After 7 days, the aqueous solution containing the diffused methanol vapor was centrifuged and separated into liquid and solid phases. The product was thrice-washed with methanol. Next, the product was dried overnight and then vacuum dried at 50 °C for 6 h.

Characterization

Powder X-ray diffraction (PXRD) was performed at room temperature under atmospheric pressure using a RIGAKU MiniFlex600. CuKalpha (wavelength 0.15418 nm) was used as an X-ray tube at 30 kV and 15 mA. The BET area and pore volume were obtained by performing nitrogen adsorption/desorption measurements at the temperature of liquid nitrogen (77 K) using a MicrotracBEL BELSORP-max. Before measurements, pretreatment was performed by heating at 50 °C for 6 h in a vacuum using a MicrotracBEL BELPREP-vac. Thermogravimetric analysis was conducted using a Shimadzu Corporation DTG-60H. Approximately 5 mg of sample was placed in an alumina cell and heated from room temperature to 600 °C at a rate of 5 °C/min. Field emission scanning electron microscope (FESEM) images were recorded on a Hitachi High-Tech S-4800. The measurement was performed at an acceleration voltage of 2.0–3.0 kV. To estimate the drug content in CD-MOF, the chemical compositions of the final product were measured by using an energy-dispersive X-ray spectrometry Emax EVOlution (Horiba) and drug concentrations of the elute were measured using a UV-visible spectrophotometer UV-1900i (Shimadzu).

The cytotoxicity of the CD-MOF carriers was evaluated by the cell viability assay using MRC-5 lung fibroblast cells (4×10^5 cells/mL), A549 alveolar epithelial cells (4×10^5 cells/mL) and Caco-2 small intestine epithelial cells (confluent).[2,3] MRC-5 and Caco-2 cells were cultured in Minimum Essential Medium (MEM; Sigma-Aldrich; St. Louis, MO, USA) and A549 cells were cultivated in Dulbecco's Modified Eagle's Medium (DMEM; Sigma-Aldrich) under 5% CO_2 at 37 °C for 24 h. Each medium was supplemented with 10% (v/v) fetal calf serum, 50 U/mL penicillin, and 50 μg/mL streptomycin. The cells were treated with a dispersion of CD-MOFs at a final concentration of 0.1–10 g/L. After 24 h of treatment, cell viability was assessed using a Cell Counting Kit-8 (Dojindo Molecular Technologies, Kumamoto, Japan) according to the manufactures' protocols. The absorbance at 450 nm was measured using a Multiskan FC microplate photometer (Thermo Fisher Scientific, Waltham, MA, USA). The cell viability (%) was calculated using the following equation:

$$\text{cell viability}(\%) = \frac{\text{abs}_{\text{sample}}}{\text{abs}_{\text{control}}} \times 100$$

where $\text{abs}_{\text{sample}}$ and $\text{abs}_{\text{control}}$ represent the absorbance with and without the addition of samples, respectively.

References

1 R. A. Smaldone, R. S. Forgan, H. Furukawa, J. J. Gassensmith, A. M. Z. Slawin, O. M. Yaghi and J. F. Stoddart, *Angew. Chem., Int. Ed.*, 2010, **49**, 8630–8634.

2 J. Y. Tse, K. Kadota, Y. Hirata, M. Taniguchi, H. Uchiyama and Y. Tozuka, *J. Drug Deliv. Sci. Technol.*, 2018, **48**, 137–144.

3 J. Y. Tse, A. Koike, K. Kadota, H. Uchiyama, K. Fujimori and Y. Tozuka, *Eur. J. Pharm. Biopharm.*, 2021, **167**, 116–126.

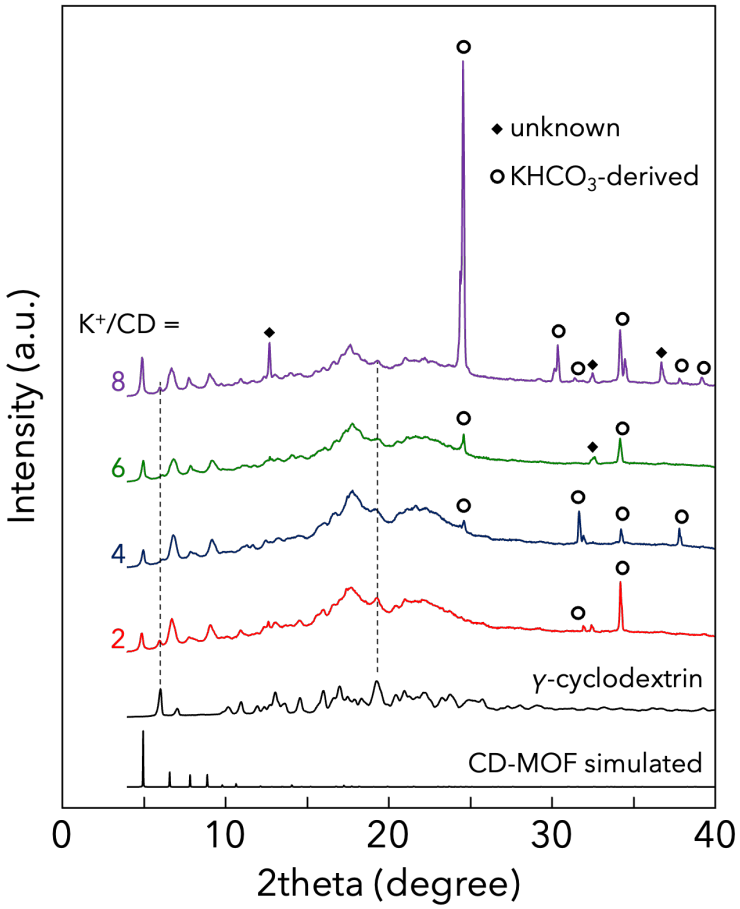

Figure S1 PXRD patterns of the products prepared without mechanochemical treatment.

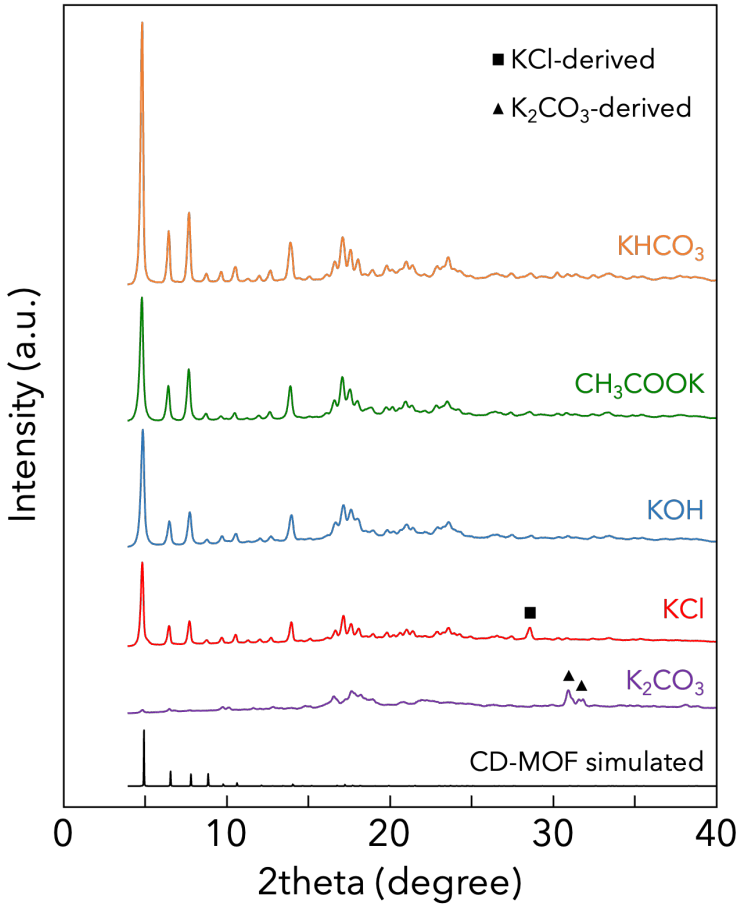

Figure S2 PXRD patterns of CD-MOFs prepared with different potassium sources ($KHCO_3$, CH_3COOK, KOH, KCl and K_2CO_3). CD-MOFs were prepared at K^+/CD = 2 by wash-free mechanochemical synthesis.

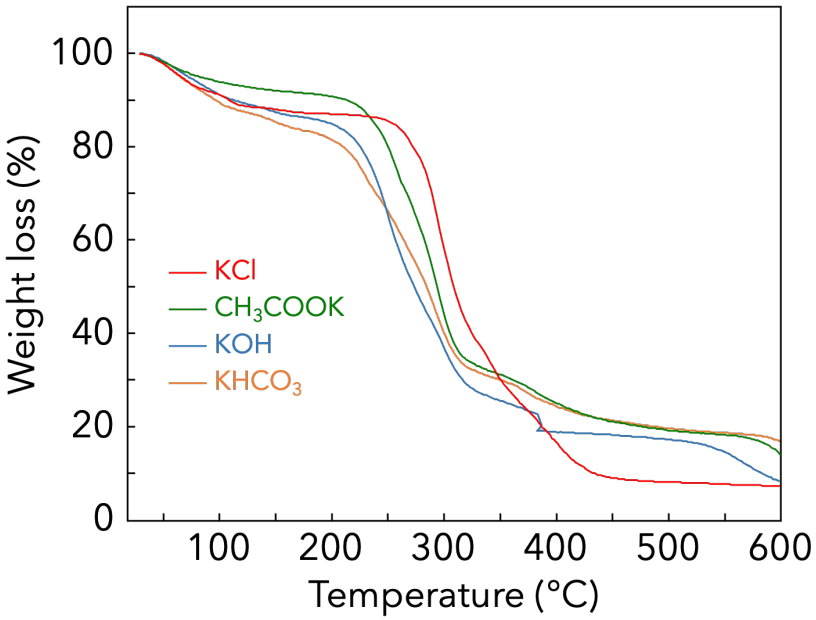

Figure S3 Thermogravimetric curves of CD-MOFs prepared using different potassium sources ($KHCO_3$, CH_3COOK, KOH and KCl). CD-MOFs were prepared at K^+/CD = 2 by wash-free mechanochemical synthesis.

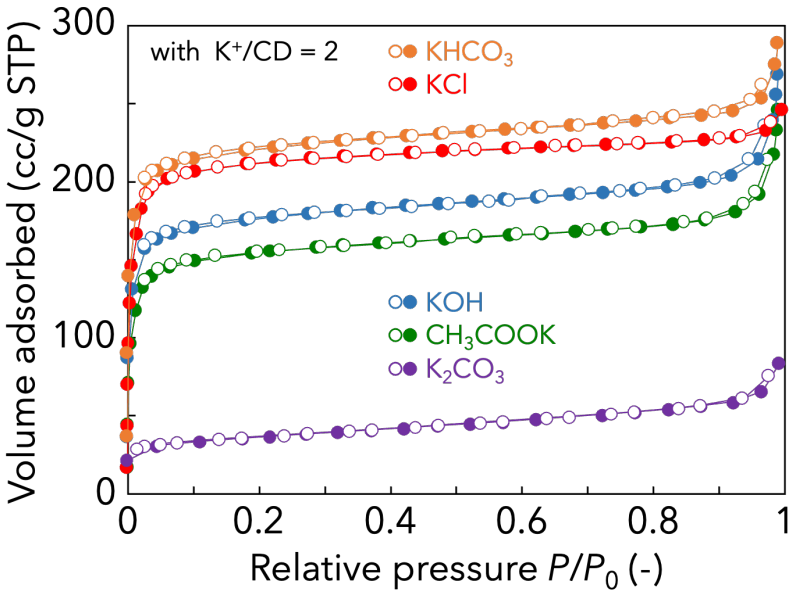

Figure S4 N_2 adsorption/desorption isotherms of CD-MOFs prepared with different potassium sources ($KHCO_3$, CH_3COOK, KOH, KCl and K_2CO_3). Before the measurements, the samples were degassed at 50 °C under vacuum for 6 h.

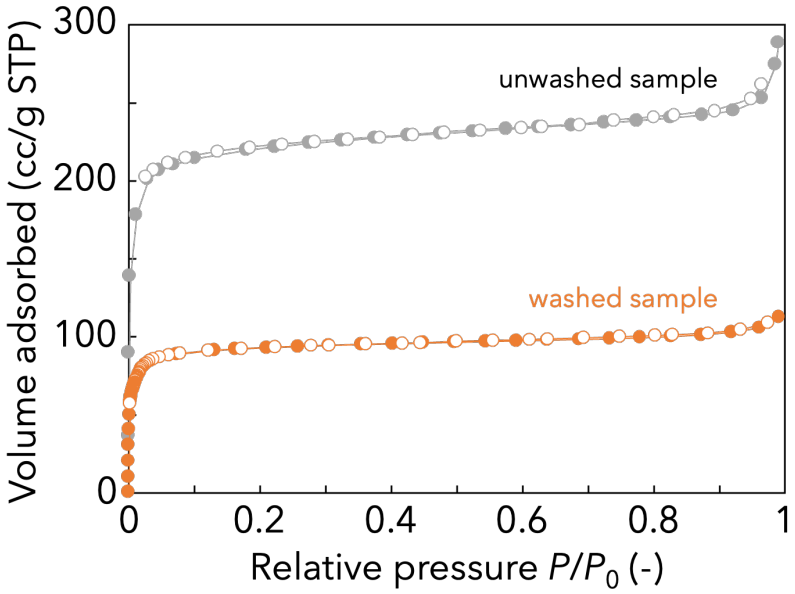

Figure S5 N_2 adsorption/desorption isotherm of the product washed after mechanochemical treatment. The product was prepared using $KHCO_3$ at K^+/CD = 2. Before the measurements, the samples were degassed at 50 °C under vacuum for 6 h.

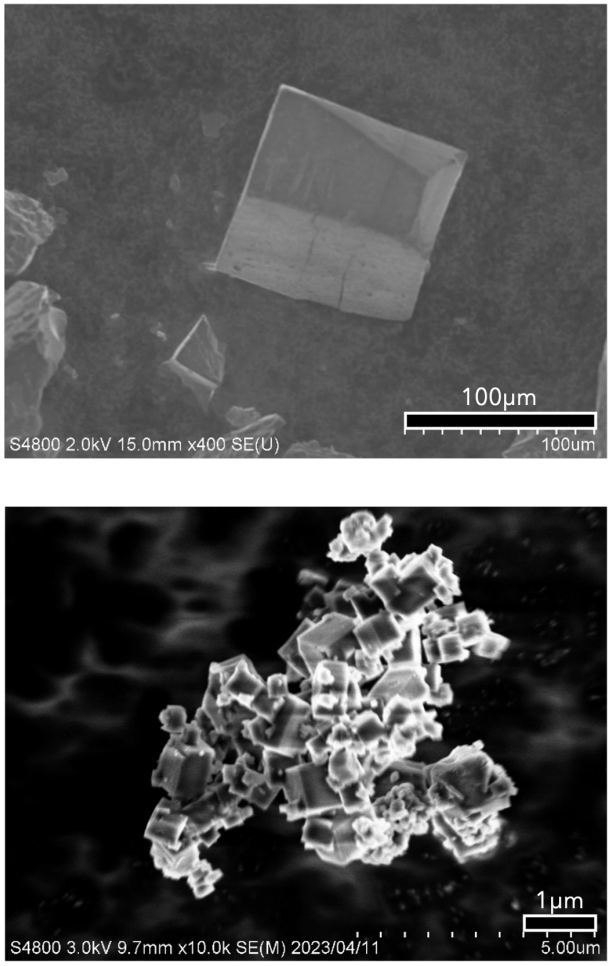

Figure S6 FESEM images of CD-MOFs prepared by (upper) conventional vapor diffusion method and (bottom) wash-free mechanochemical synthesis. CD-MOF was prepared using $KHCO_3$ at K^+/CD = 2 by wash-free mechanochemical synthesis.

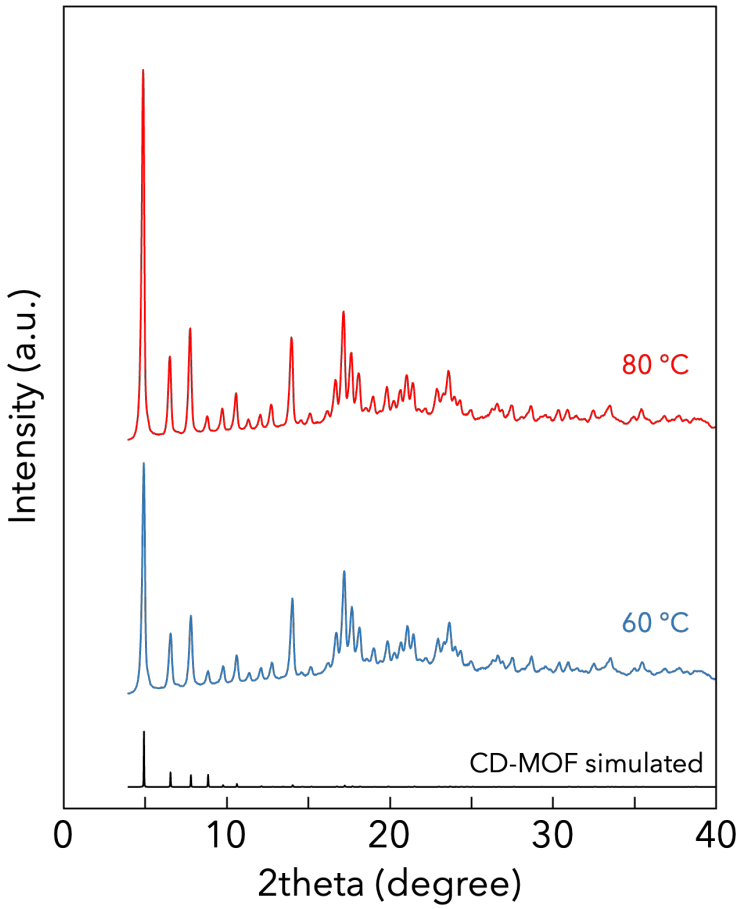

Figure S7 PXRD patterns of CD-MOFs prepared using KCl at K^+/CD = 1.5 by wash-free mechanochemical synthesis. After the mechanochemical step, the products were dried at 60 °C or 80 °C.

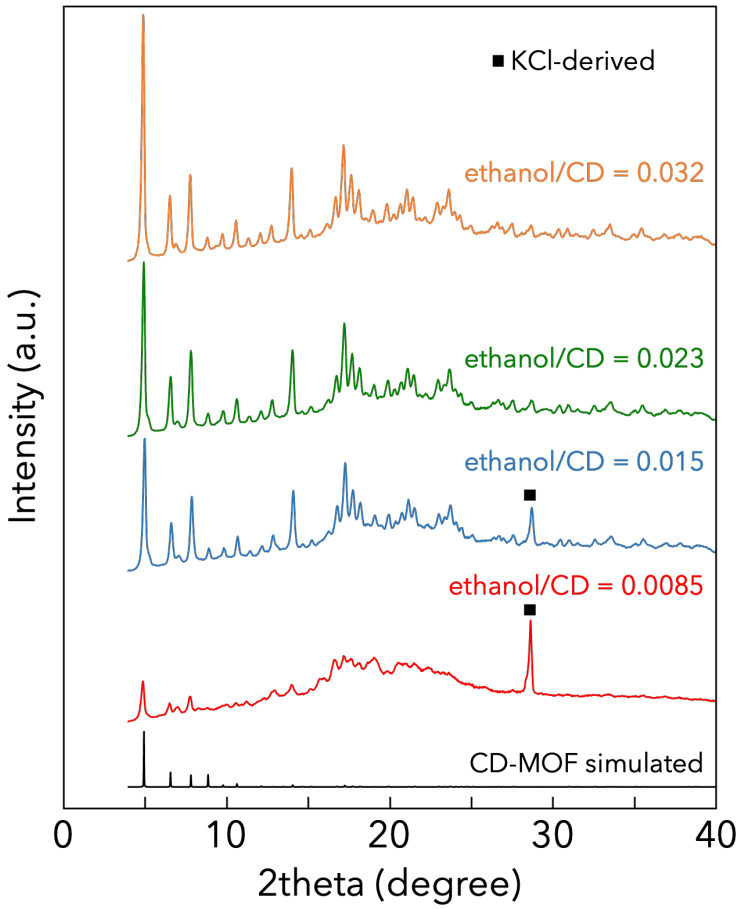

Figure S8 PXRD patterns of CD-MOFs prepared by wash-free mechanochemical synthesis with different ethanol/CD ratios using KCl at K^+/CD = 1.

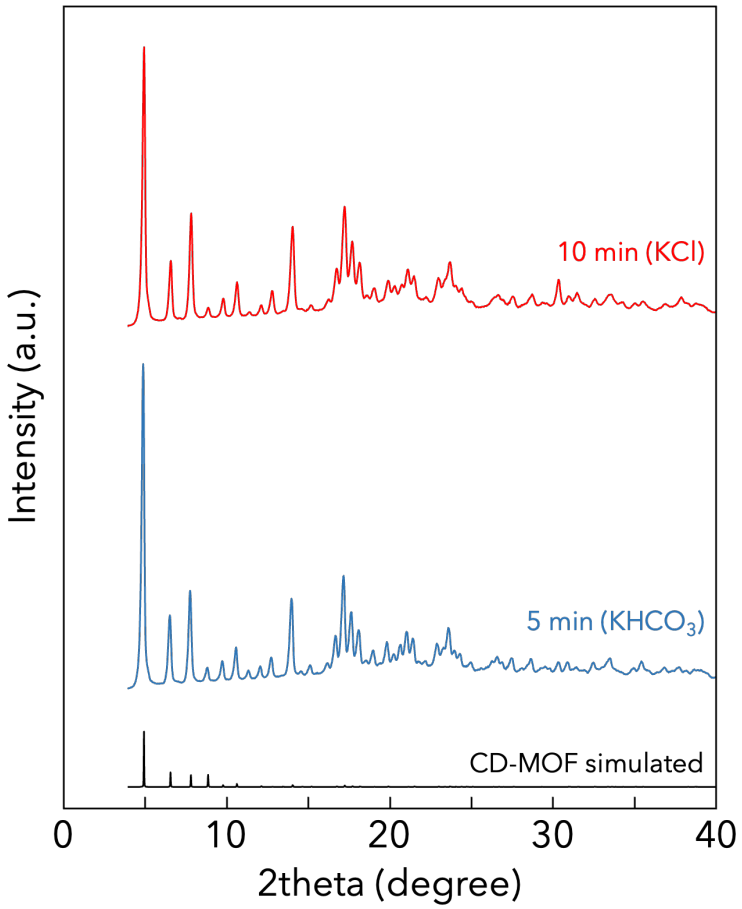

Figure S9 PXRD patterns of CD-MOFs prepared at different mechanochemical treatment times. CD-MOFs were prepared using KCl or $KHCO_3$ at K^+/CD = 1.5.

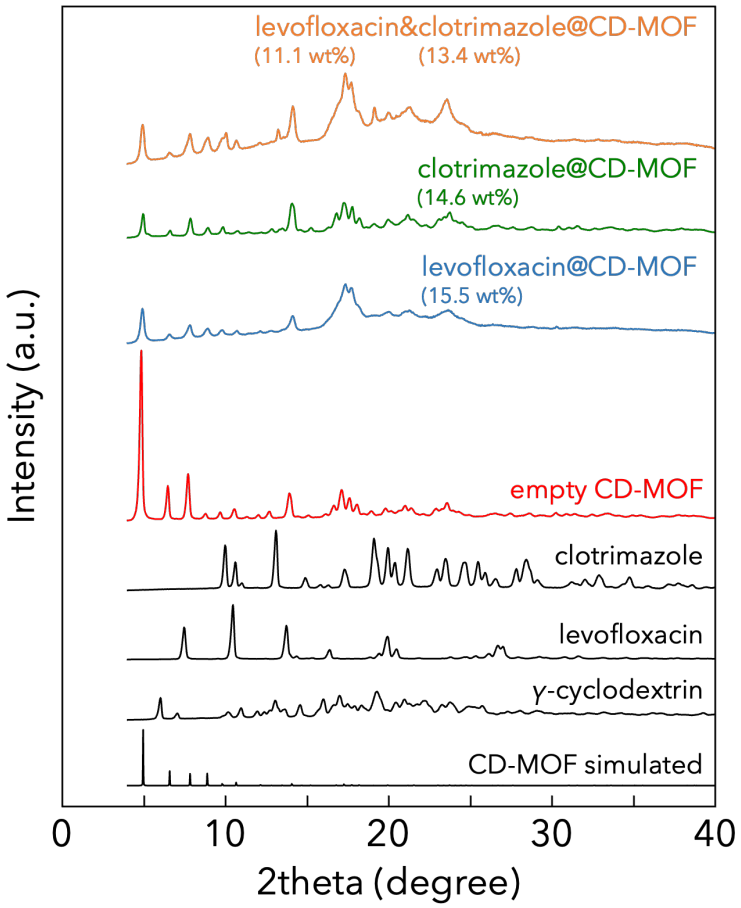

Figure S10 PXRD patterns of CD-MOF and drug-encapsulated CD-MOF. CD-MOFs were prepared by wash-free mechanochemical synthesis using $KHCO_3$ at K^+/CD = 2.