

Supporting information

Structural Analysis of Anti-Retroviral Drug Raltegravir and its Potential Impurity C: Investigation of Solubility and Stability

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Table S1. Polymorph screening (SCXRD analysis)

Sample Code	Morphology	Unit Cell Parameters	Conclusion
RLT (hexane-anisole)	Plate	a = 8.484Å, b = 11.742Å, c = 12.325Å α = 110.248°, β = 108.845°, γ = 92.542° V = 1048.24Å ³	RLT hydrate
RLT (hexane-isopropanol)	Plate	a = 8.874Å, b = 11.158Å, c = 12.654Å α = 110.854°, β = 108.245°, γ = 92.624° V = 1047.35Å ³	RLT hydrate
	Block	a = 8.954Å, b = 11.264Å, c = 12.389Å α = 110.650°, β = 108.084°, γ = 92.357° V = 1049.19Å ³	RLT hydrate
RLT (THF-water)	Plate	a = 8.391Å, b = 11.024Å, c = 12.409Å α = 110.278°, β = 108.924°, γ = 92.640° V = 1046.05Å ³	RLT hydrate
RLT (anisole-n-Propanol)	Plate	a = 8.135Å, b = 11.359Å, c = 12.254Å α = 110.015°, β = 108.586°, γ = 92.259° V = 1048.55Å ³	RLT hydrate
RLT (Ethyl acetate)	Plate	a = 8.369Å, b = 11.279Å, c = 12.182Å α = 110.111°, β = 108.872°, γ = 92.105° V = 1047.22Å ³	RLT hydrate
RLT (Methanol)	Plate	a = 8.524Å, b = 11.242Å, c = 12.102Å α = 110.175°, β = 108.864°, γ = 92.745° V = 1049.57Å ³	RLT hydrate
RLT (anisole-hexane 2)	Plate	a = 8.354Å, b = 11.455Å, c = 12.752Å α = 110.853°, β = 108.532°, γ = 92.185° V = 1047.28Å ³	RLT hydrate
RLT (MeOH recrystallized)	Plate	a = 8.146Å, b = 11.456Å, c = 12.453Å α = 110.835°, β = 108.756°, γ = 92.756° V = 1047.78Å ³	RLT hydrate

Table S2. Hydrogen bond geometry (Å, °) of RLT and impurity phases

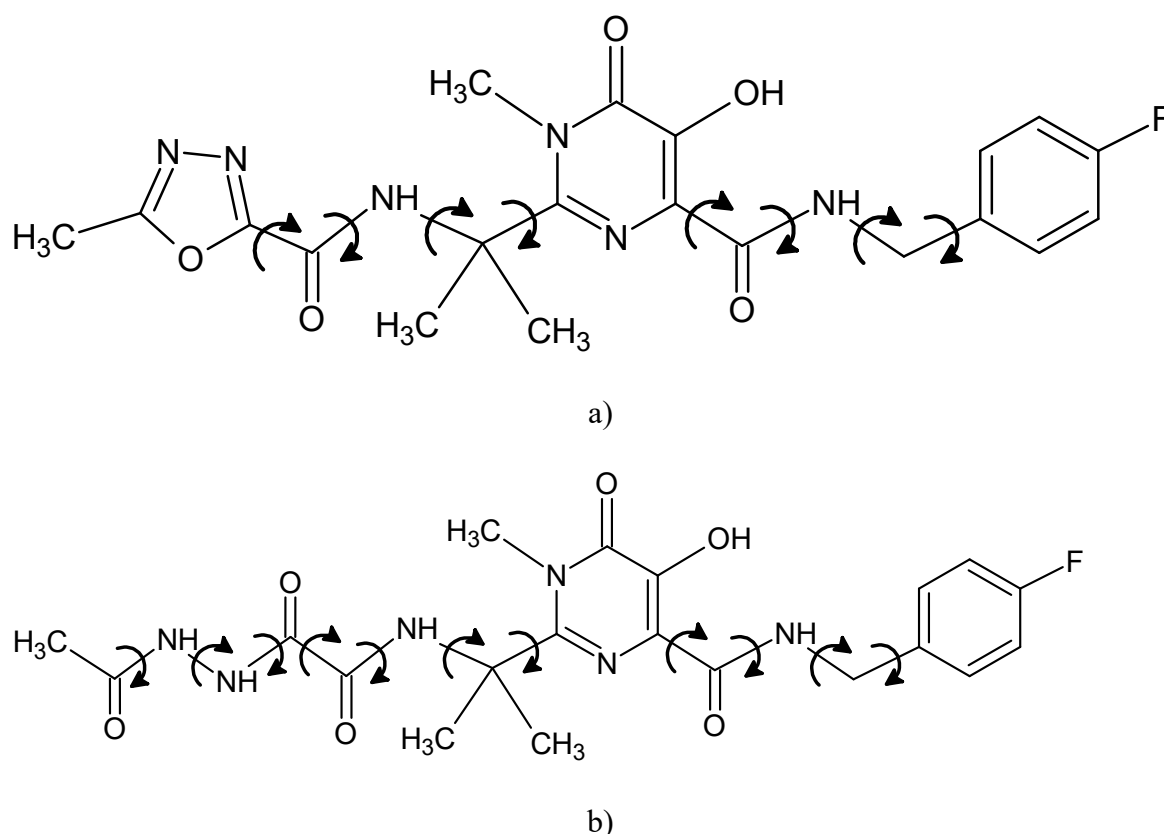
	D-H...A	D-H/ Å	H...A/Å	D...A/Å	D-H...A/°	Symmetry code
Form A	N1-H1...O2	0.90	2.06	2.8977(3)	154	x,3/2-y,1/2+z
	C18-H18C...O5	0.96	2.57	3.4200(4)	147	-x,1-y,1-z
	C20-H20A...F1	0.96	2.48	3.2750(4)	140	-x,-1/2+y,3/2-z
Hydrate (Reported)	N1-H1...O5	0.88	2.23	2.9697(2)	142	2-x,-y,1-z
	O1W-H1WA ...O3	0.85	2.33	3.0130(2)	138	1-x,-y,1-z
	O1W-H1WA ...O4	0.85	2.51	3.2488(2)	146	1-x,-y,1-z

	O1W–H1WB…O2	0.85	2.04	2.8690(2)	164	1-x,1-y,1-z
	N4–H4A…O1W	0.88	3.0735(2)	3.0735(2)	126	1+x,y,z
	C7–H7A…O1W	0.99	3.2408(2)	3.2408(2)	124	1+x,y,z
	C10–H10…O5	0.95	2.50	3.3930(3)	157	2-x,-y,2-z
	C20–H20A…O4	0.98	2.46	3.3941(3)	160	1-x,-y,1-z
	C20–H20B…N6	0.98	2.50	3.4218(3)	157	1-x,-y,-z
Impurity C	N1–H1…O1	0.86	2.14	2.9917(4)	169	1-x,2-y,1-z
	O4–H4…O2	0.82	2.49	2.8193(3)	105	-x,2-y,-z
	N4–H4A…O6	0.86	2.56	3.0536(4)	117	-x,2-y,1-z
	N5–H5…O2	0.86	1.94	2.7652(3)	159	-x,2-y,1-z
	N6–H6…O3	0.86	2.19	3.0101(4)	159	x,y,1+z
	C7–H7B…O6	0.97	2.44	3.1026(4)	125	-x,2-y,1-z
	C20–H20A…F1	0.96	2.9198(4)	2.9198(4)	105	1+x,1+y,z
	C20–H20B…O3	0.96	2.47	3.3240(4)	148	1-x,2-y,-z
Impurity C1	N1–H1…O1	0.86	2.11	2.9337(6)	159	-x,y,-1/2-z
	N5–H5…O2	0.86	2.02	2.8053(6)	154	-x,y,1/2-z
	N6–H6…O3	0.89	1.87	2.7099(6)	157	-x,-y,-z
	C17–H17B…O6	0.96	2.48	3.4068(7)	162	-1/2-x,1/2-y,-z
	C19–H19C…F1	0.96	2.55	3.4651(7)	159	1-x,y,1/2-z
	C12–H12…O5	0.93	2.39	3.2218(7)	149	1-x,-y,1-z

Crystal structure determination and Rietveld refinement of RLT Form A and impurity C from XRPD patterns.

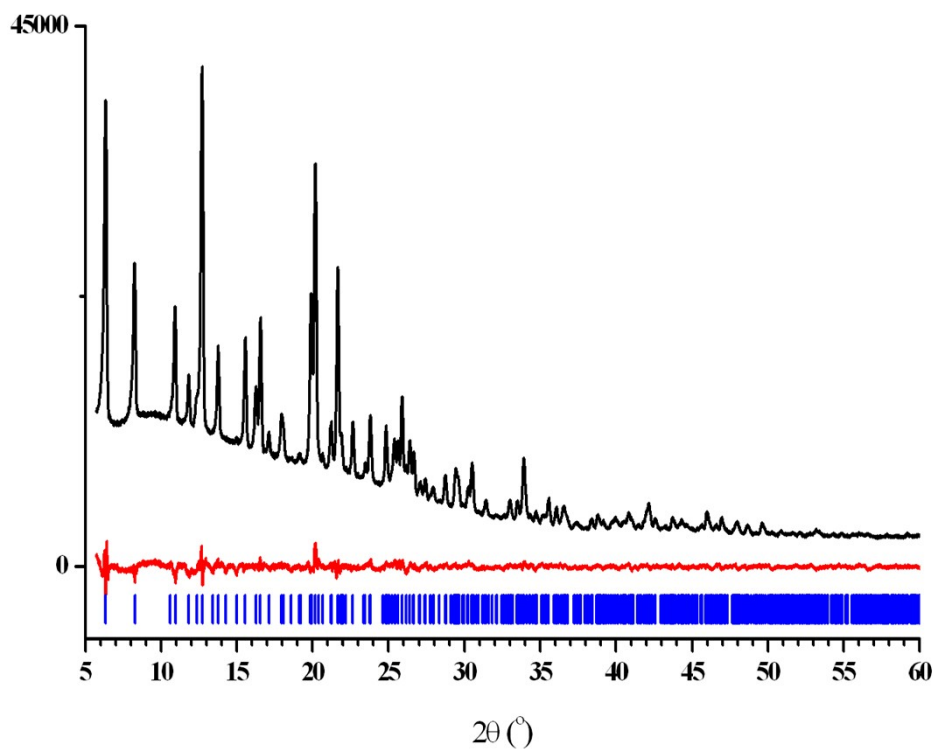
Three indexing programs: TREOR90,¹ ITO² and AUTOX.^{3,4} were used to index both powder patterns of RLT Form A and impurity C. The monoclinic and triclinic unit cell parameters were unambiguously assigned for RLT Form A and impurity C compounds, respectively, by all programs as well as space group $P2_1/c$ was chosen for the former compound. The unit-cell parameters and space groups ($P-1$ for impurity C) were further tested using a Pawley fit⁵ and confirmed by crystal structure solutions.

The crystal structures were further solved by applying the simulated annealing technique⁶ implemented in the program MRIA.⁷ In both compounds, the asymmetric unit contained one molecule. Therefore, in simulated annealing runs we used molecular models without H atoms shown in Scheme S1 with eight internal degrees of freedom (DOF, torsion angles shown by arrows in Scheme S1) for RLT molecule (Scheme S1, top) and eleven internal DOF for impurity C molecule (Scheme S1, bottom).

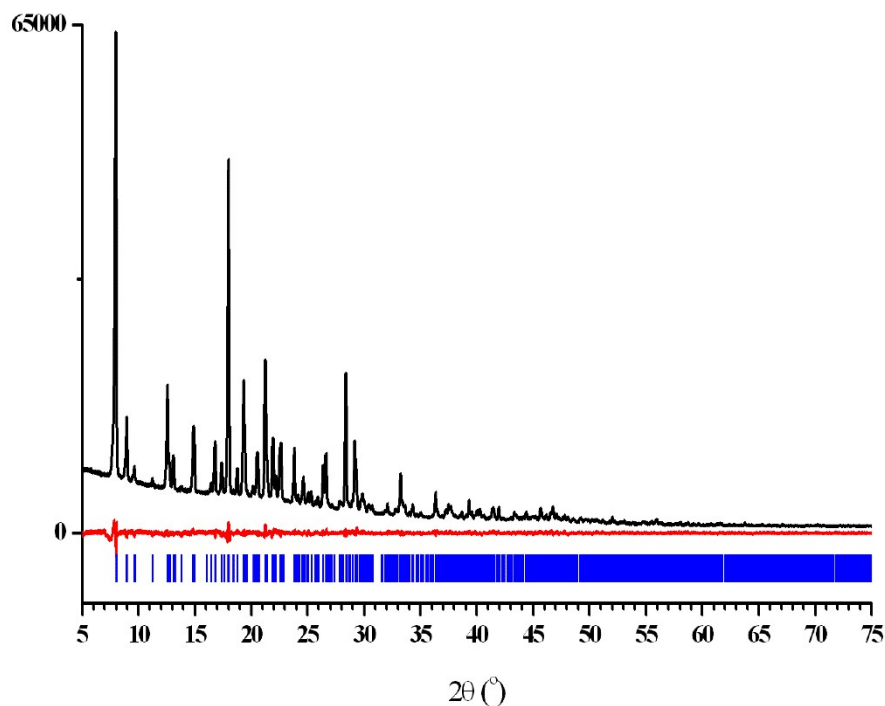


Scheme S1. Molecular diagrams of RLT a) Form A and b) impurity C with degrees of freedom.

So in the direct space search for structural motif, the total number of DOF for RLT Form A was equal to 14, and for impurity C the number of DOF was equal to 17. The structural parameters were further fitted with the program *MRIA* in the bond-restrained Rietveld refinement using a split-type pseudo-Voigt peak profile function.⁸ The observed anisotropy of diffraction line broadening was approximated by a quartic form in hkl . Restraints were applied to the intramolecular bond lengths and contacts ($< 2.8 \text{ \AA}$), the strength of the restraints was a function of interatomic separation and, for intramolecular bond lengths, corresponded to r.m.s. deviation 0.02 \AA . Additional restraints were applied to the planarity of five- and six-membered rings with the attached atoms, with the maximal allowed deviation from the mean plane 0.03 \AA . The diffraction profiles after the final bond-restrained Rietveld refinement are shown in Figure S1.



(a)



(b)

Figure S1. The Rietveld plots after the final bond-restrained refinement for a) RLT-Form A and b) Impurity-C, showing the experimental and difference diffraction profiles as black (top) and red (bottom) curves, respectively. The vertical blue bars correspond to the calculated positions of the Bragg peaks.

References.

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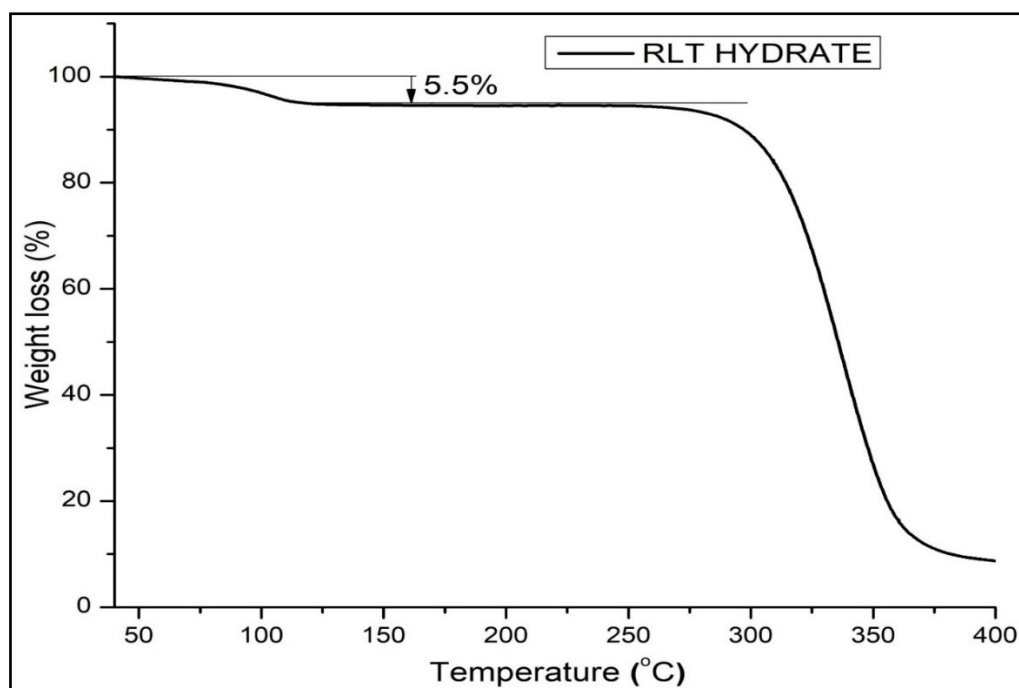
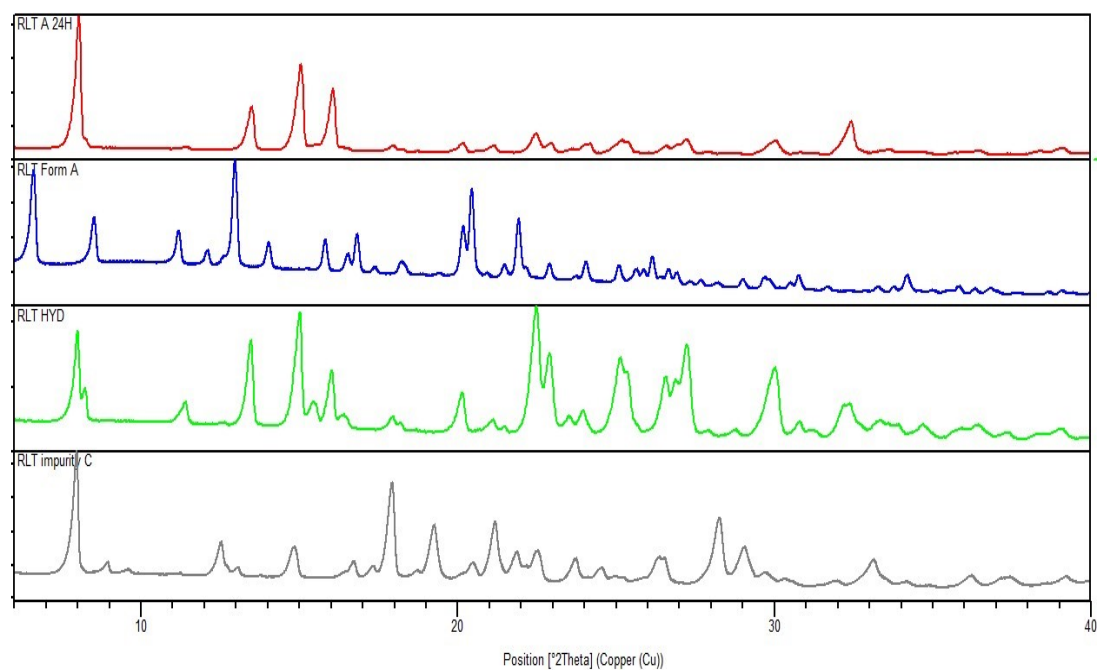
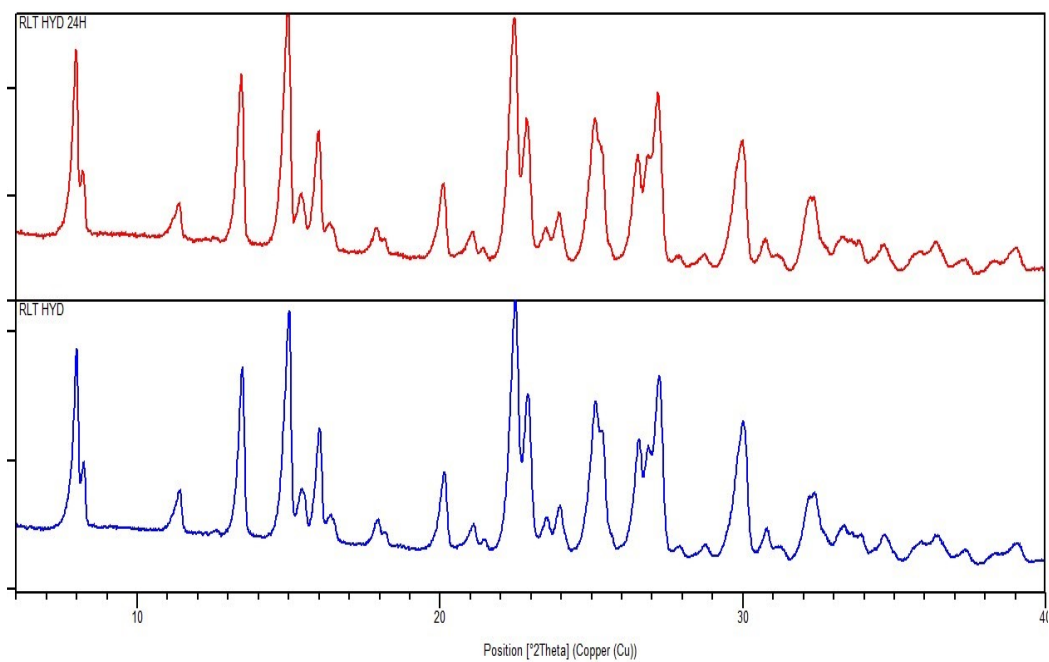


Figure S3. TGA thermogram of RLT hydrate confirms 1.4 equivalent water molecule present. Experimental little higher than the monohydrate (calculated 3.9%) may be due to absorbed moisture.

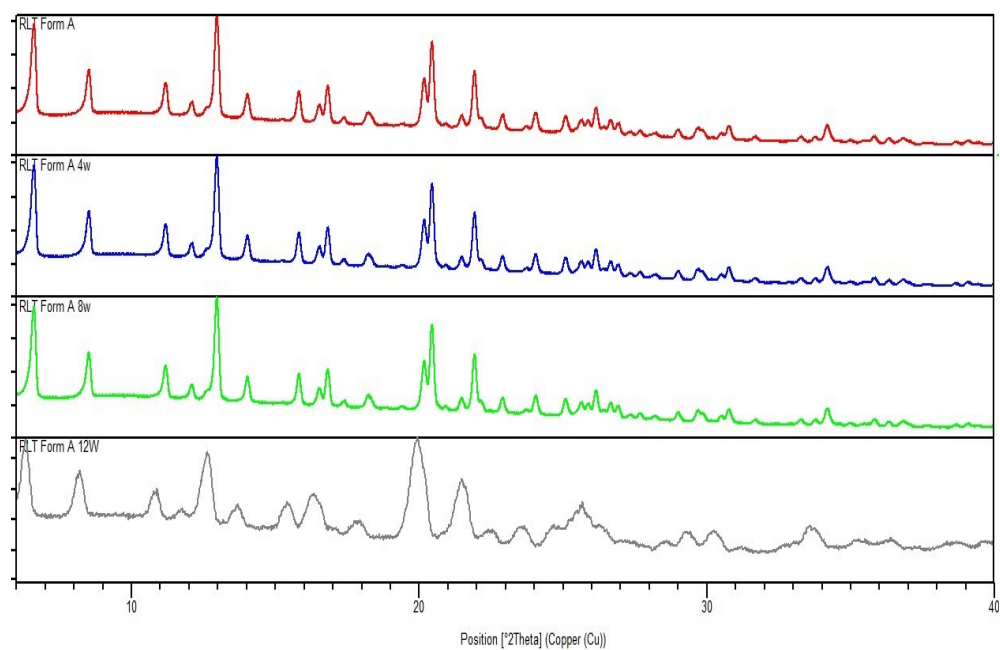


(a)

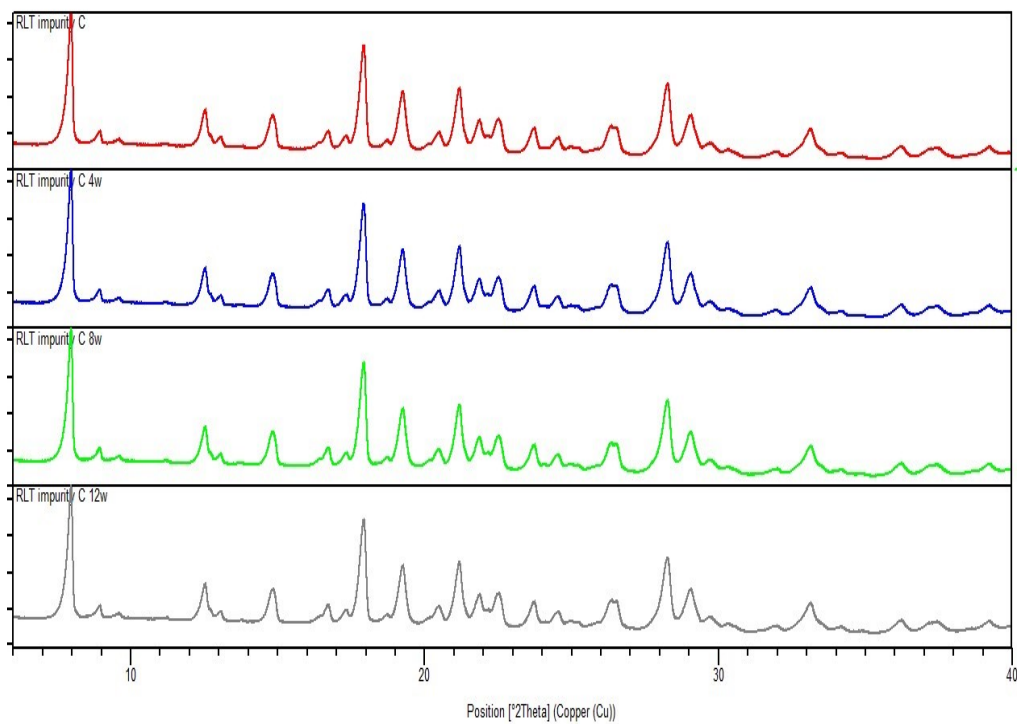


(b)

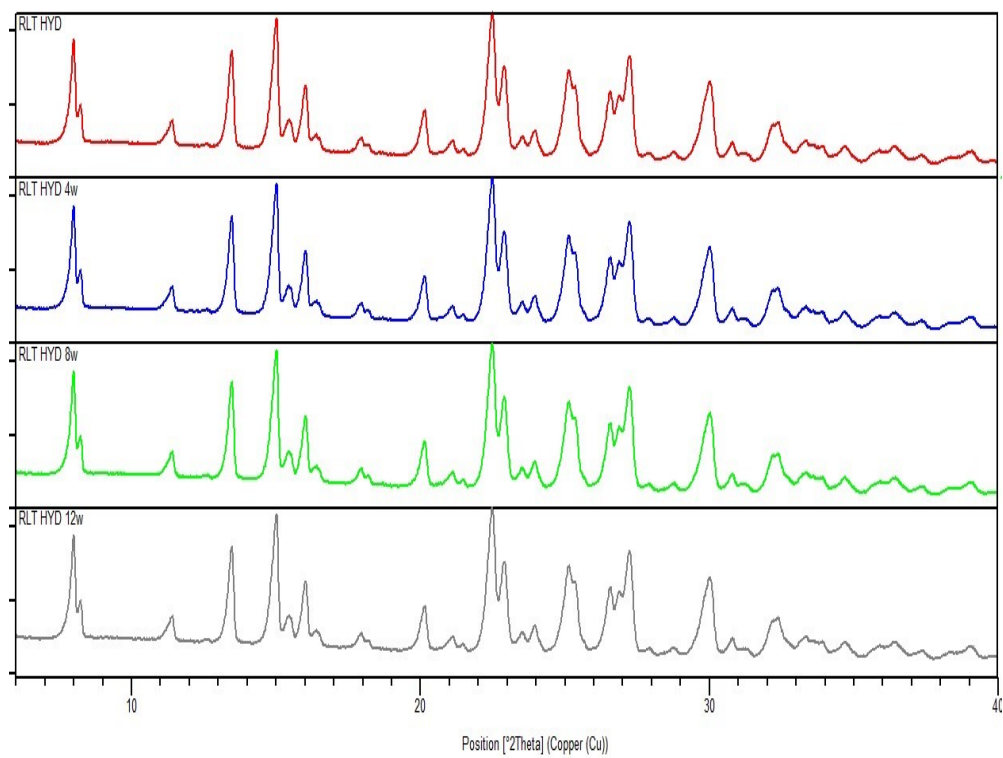
Figure S4. Phase transformation of RLT a) Form A, b) Hydrate using PXRD confirmed anhydrous Form A converted to hydrate during 24h solubility experiment.



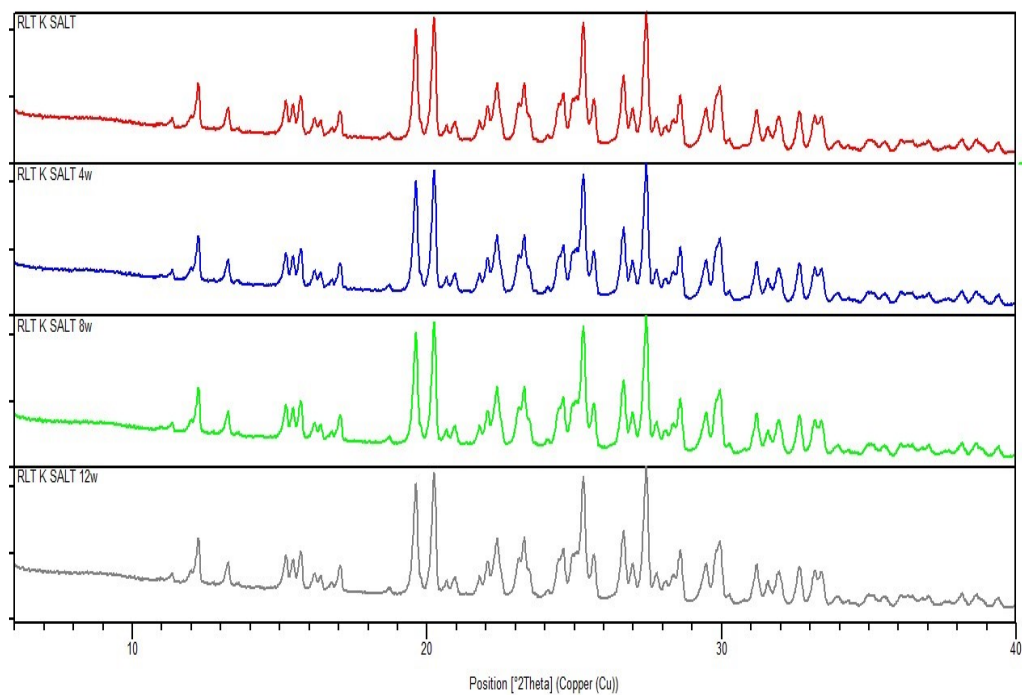
(a)



(b)

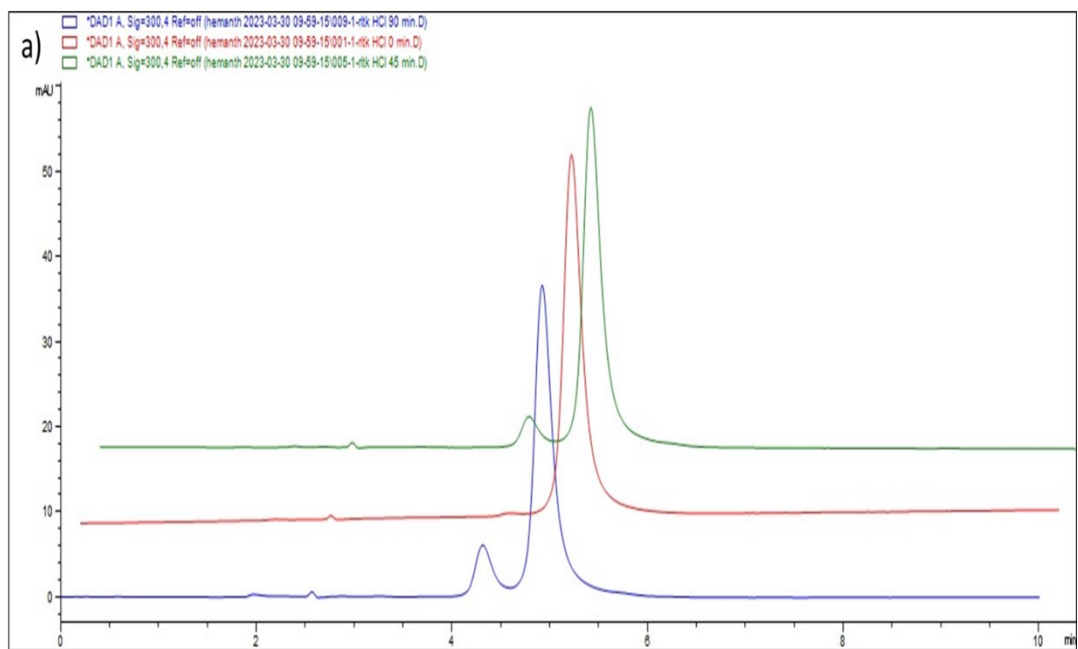


(c)

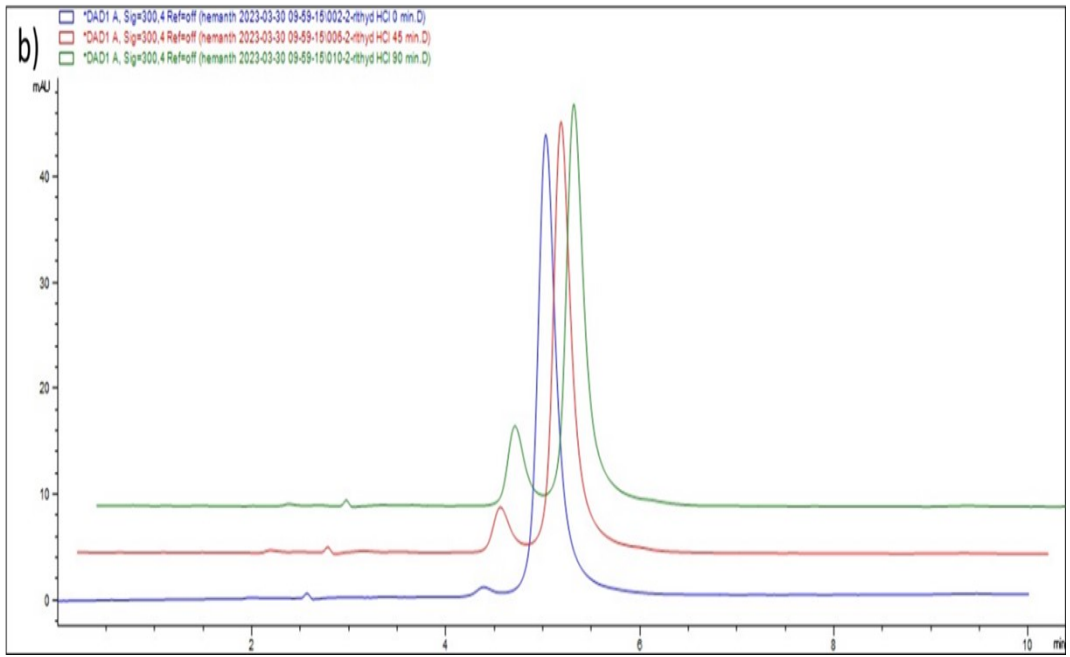


(d)

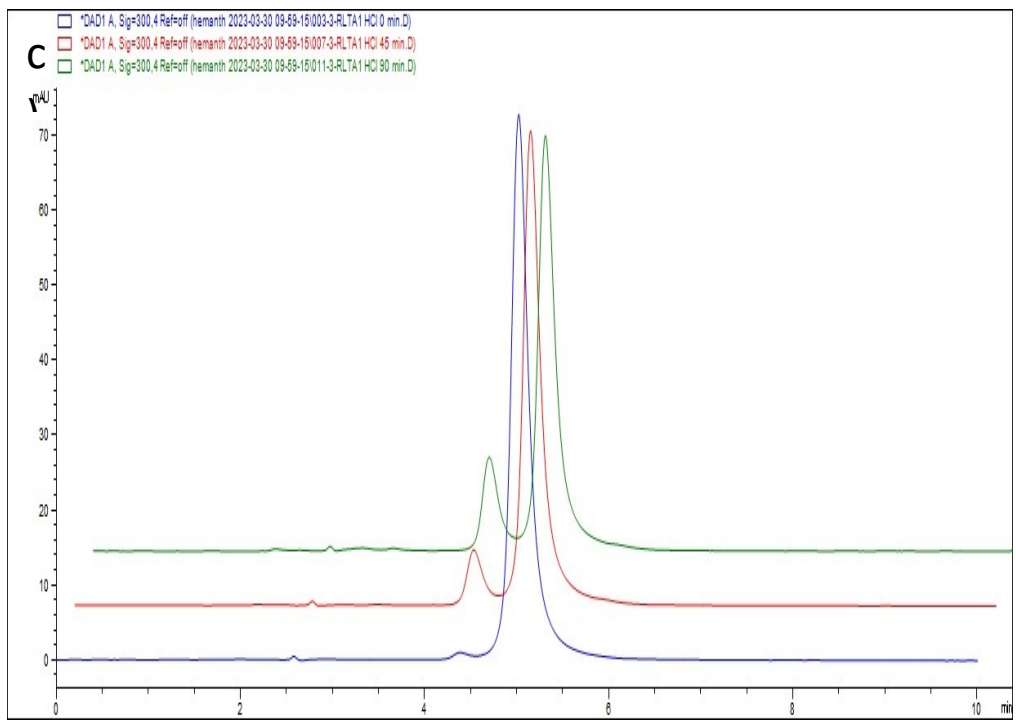
Figure S5. PXRD comparison of RLT a) Form A, b) impurity C, c) Hydrate, and d) K salt up to 12 weeks in 35 ± 5 °C and $75\pm 5\%$ relative humidity that confirm the stability of all the RLT solid forms and impurity C.



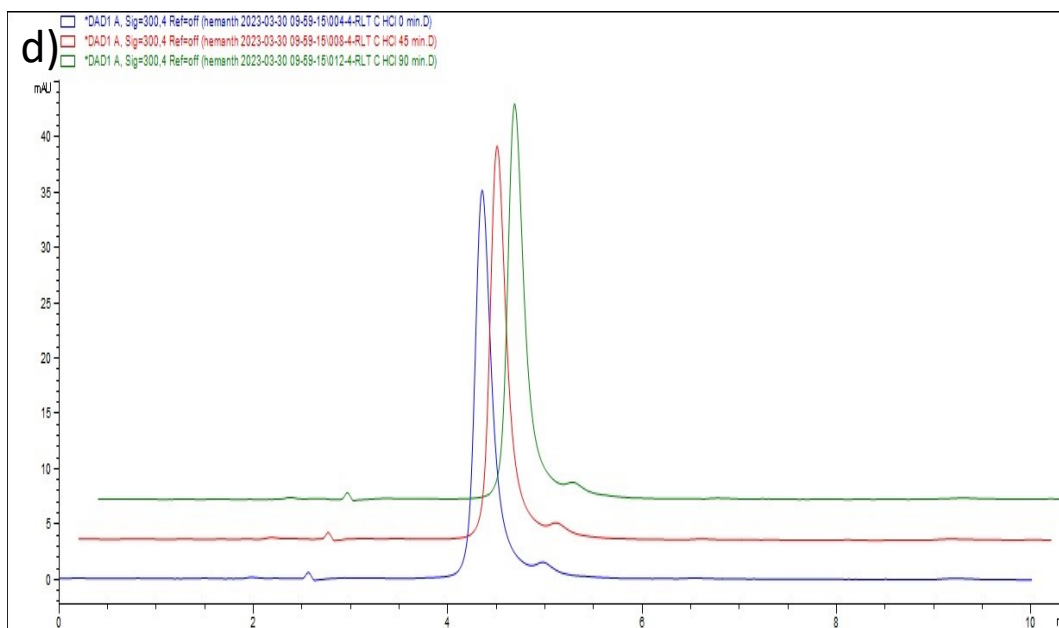
(a)



(b)



(c)



(d)

Figure S6. Overlay of HPLC chromatograms at 0, 45 and 90 min of (a) RLT K, (b) RLT hydrate, (c) RLT A, and (d) Impurity C.