A novel naproxen potassium dihydrate: Single-crystal structure and solid-state characterization of the dihydrate and its anhydrous form with improved dissolution properties

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$C_{14}H_{14}O_3 + KOH \rightarrow C_{14}H_{13}O_3K \cdot 2H_2O \downarrow$*	**Eq. S1**

*Crystallized from a hydro-alcoholic (50:50) solution

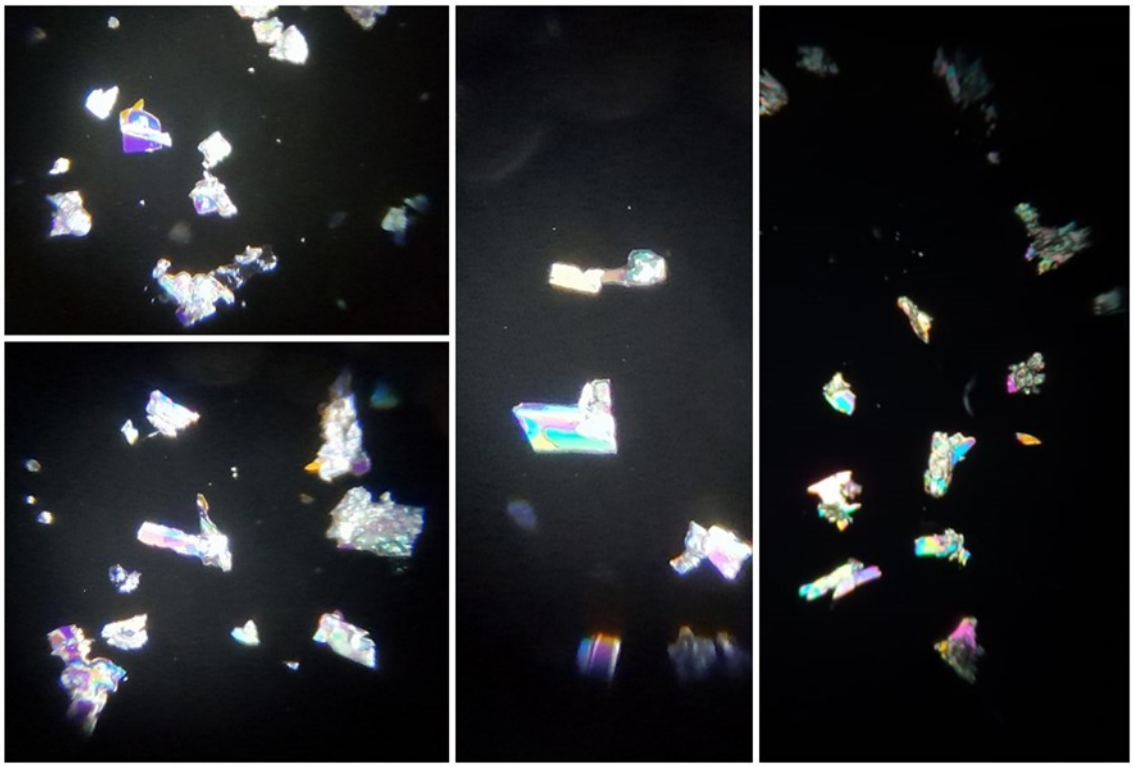

Figure S1. Different views of NP crystals exhibiting birefringence under polarized light microscopy at a total magnification of 55×.

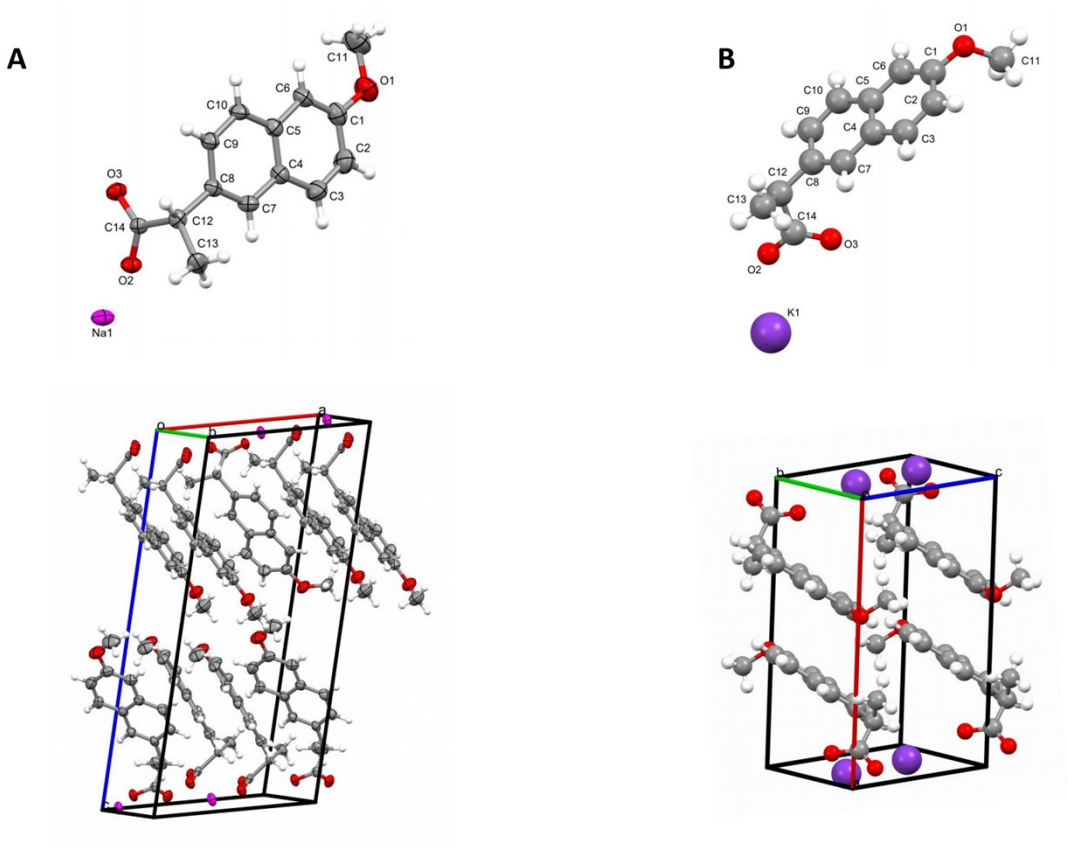

Figure S2. Asymmetric unit showing one naproxen anion, one counterion for NS (A) and of NP-ANH (B).

Table S1. Mass composition (mg) of the excipient matrix used for tablet formulation.

Excipient	Amount (mg)
Corn starch	77.8
Povidone	30.4
Croscarmellose sodium	21.2
Colloidal silicon dioxide	1.42
Magnesium stearate	3.54
Hydroxypropylmethylcellulose	9.00
Polyethylene glycol 6000	1.20
Sodium saccharin	0.345
Tween 80	0.495
Titanium dioxide	4.60

Table S2. Spatial details. Atomic coordinates and equivalent isotropic displacement parameters (Å2) for NP-DH.

	x/a	**y/b**	**z/c**	**U (eq)**
K1	0.7077 (3)	0.3550 (3)	0.54259 (5)	0.0449 (5)
O1	0.0483 (12)	0.0817 (11)	0.5268 (2)	0.059 (2)
O2	0.0256 (10)	0.6426 (11)	0.52403 (16)	0.0463 (15)
O3	0.4408 (9)	0.6673 (8)	0.56051 (12)	0.0371 (13)
O4	0.5013 (9)	0.9873 (8)	0.54479 (13)	0.0397 (13)
O5	0.8075 (11)	0.9411 (8)	0.72413 (14)	0.0470 (15)
C1	0.5052 (12)	0.8436 (13)	0.56647 (18)	0.0305 (17)
C2	0.5928 (12)	0.8981 (11)	0.60300 (19)	0.0294 (18)
C3	0.4022 (15)	0.0279 (12)	0.6197 (2)	0.043 (2)
C4	0.6633 (12)	0.7150 (11)	0.62409 (18)	0.0254 (17)
C5	0.8683 (12)	0.6122 (12)	0.61472 (19)	0.0331 (19)
C6	0.9420 (13)	0.4441 (12)	0.63226 (18)	0.0323 (19)
C7	0.8183 (12)	0.3646 (12)	0.66004(17)	0.0302 (16)
C8	0.6127 (11)	0.4645 (11)	0.67001 (18)	0.0263 (17)
C9	0.5403 (12)	0.6382 (13)	0.65109 (18)	0.0325 (17)
C10	0.4881 (13)	0.3879 (12)	0.69868 (19)	0.0349 (18)
C11	0.5605 (14)	0.2150 (12)	0.71565 (19)	0.036 (2)
C12	0.7610 (12)	0.1114 (12)	0.70551 (18)	0.0320 (18)
C13	0.8871 (13)	0.1855 (11)	0.67829 (18)	0.0317 (18)
C14	0.9995 (16)	0.8209 (13)	0.7132 (2)	0.049 (2)

U(eq) is defined as one third of the trace of the orthogonalized U*ij* tensor

Table S3. Bond lengths [Å] and angles [º] for NP-DH.

Bond lengths	Values (E) [Å]
K1-O3	2.662 (6)
K1-O2	2.737 (7)
K1-O1#2	2.866 (8)
K1-C1	3.534 (8)
K1-K1#3	4.605 (3)
K1-H2A	2.99 (9)
O1-H1A	0.77 (11)
O2-H2A	0.90 (9)
O4-C1	1.260 (9)
O5-C14	1.432 (10)
C2-C4	1.507 (10)
C2-H2	0.98
C3-H3B	0.96
C4-C9	1.362 (10)
C5-C6	1.362 (11)
C6-C7	1.394 (10)
C7-C8	1.418 (9)
C8-C10	1.416 (10)
C9-H9	0.93
C10-H10	0.93
C11-H11	0.93
C13-H13	0.93
C14-H14B	0.96
K1-O4#1	2.693 (6)
K1-O1	2.741 (7)
K1-C5	3.389 (8)
K1-K1#2	4.605 (3)
K1-H1B	3.03 (11)

O1-H1B	0.81 (11)
O2-H2B	0.82 (10)
O3-C1	1.236 (9)
O5-C12	1.355 (9)
C1-C2	1.543 (10)
C2-C3	1.541 (10)
C3-H3A	0.96
C3-H3C	0.96
C4-C5	1.418 (10)
C5-H5	0.93
C6-H6	0.93
C7-C13	1.426 (10)
C8-C9	1.417 (10)
C10-C11	1.375 (11)
C11-C12	1.406 (10)
C12-C13	1.372 (10)
C14-H14A	0.96
C14-H14C	0.96

Bond angle	**Value[°] (E)**
O3-K1-O4#1	114.72 (18)
O4#1-K1-O2	157.80 (19)
O4#1-K1-O1	75.31 (19)
O3-K1-O1#3	86.71 (18)
O2-K1-O1#3	82.8 (2)
O3-K1-C5	64.22 (17)
O2-K1-C5	71.74 (19)
O1#3-K1-C5	141.9 (2)
O4#1-K1-C1	130.74 (17)
O1-K1-C1	153.0 (2)
C5-K1-C1	55.04 (18)

O4#1-K1-K1#3	58.20 (12)
O1-K1-K1#3	95.93 (18)
C5-K1-K1#3	155.63 (13)
O3-K1-K1#4	141.72 (14)
O2-K1-K1#4	65.82 (14)
O1#3-K1-K1#4	65.16 (16)
C1-K1-K1#4	131.93 (14)
O3-K1-H1B	175.23 (2)
O2-K1-H1B	99.15 (2)
O1#3-K1-H1B	95.12 (2)
C1-K1-H1B	168.25 (2)
K1#4-K1-H1B	43.36 (2)
O4#1-K1-H2A	143.0 (18)
O1-K1-H2A	77.3 (18)
C5-K1-H2A	89.1 (18)
K1#3-K1-H2A	101.0 (18)
H1B-K1-H2A	90.1 (3)
K1-O1-H1B	103.1 (8)
K1-O1-H1A	123.3 (9)
H1B-O1-H1A	128.2 (10)
K1-O2-H2A	98.(6)
C1-O3-K1	126.1 (5)
C12-O5-C14	116.9 (6)
O3-C1-C2	119.2 (6)
O3-C1-K1	37.5 (4)
C2-C1-K1	109.8 (4)
C4-C2-C1	113.6 (6)
C4-C2-H2	107.6
C1-C2-H2	107.6
C2-C3-H3B	109.5

C2-C3-H3C	109.5
H3B-C3-H3C	109.5
C9-C4-C2	124.4 (7)
C6-C5-C4	121.5 (7)
C4-C5-K1	102.3 (4)
C4-C5-H5	119.3
C5-C6-C7	121.5 (7)
C7-C6-H6	119.3
C6-C7-C13	122.9 (7)
C10-C8-C9	122.4 (7)
C9-C8-C7	118.8 (7)
C4-C9-H9	118.8
C11-C10-C8	120.5 (7)
C8-C10-H10	119.7
C10-C11-H11	119.4
O5-C12-C13	126.3 (7)
C13-C12-C11	119.2 (7)
C12-C13-H13	119.3
O5-C14-H14A	109.5
H14A-C14-H14B	109.5
H14A-C14-H14C	109.5
O3-K1-O2	86.23 (19)
O3-K1-O1	169.4 (2)
O2-K1-O1	84.3 (2)
O4#1-K1-O1#3	90.82 (19)
O1-K1-O1#3	96.92 (18)
O4#1-K1-C5	122.81 (18)
O1-K1-C5	108.0 (2)
O3-K1-C1	16.42 (16)
O2-K1-C1	70.77 (19)

O1#3-K1-C1	90.28 (19)
O3-K1-K1#3	92.63 (11)
O2-K1-K1#3	116.49 (16)
O1#3-K1-K1#3	33.92 (15)
C1-K1-K1#3	104.24 (12)
O4#1-K1-K1#4	92.18 (13)
O1-K1-K1#4	35.70 (17)
C5-K1-K1#4	124.19 (13)
K1#3-K1-K1#4	78.46 (7)
O4#1-K1-H1B	60.1 (2)
O1-K1-H1B	15.9 (2)
C5-K1-H1B	116.7 (2)
K1#3-K1-H1B	86.5 (2)
O3-K1-H2A	94.9 (18)
O2-K1-H2A	17.4 (18)
O1#3-K1-H2A	68.3 (18)
C1-K1-H2A	81.4 (18)
K1#4-K1-H2A	51.7 (18)
K1-O1-K1#4	110.4 (3)
K1#4-O1-H1B	103.3 (8)
K1#4-O1-H1A	82.5 (9)
K1-O2-H2B	110.1 (7)
H2B-O2-H2A	108.0 (9)
C1-O4-K1#2	132.9 (5)
O3-C1-O4	124.6 (7)
O4-C1-C2	116.2 (7)
O4-C1-K1	120.6 (5)
C4-C2-C3	114.1 (6)
C3-C2-C1	105.9 (6)
C3-C2-H2	107.6

C2-C3-H3A	109.5
H3A-C3-H3B	109.5
H3A-C3-H3C	109.5
C9-C4-C5	117.6 (7)
C5-C4-C2	118.0 (7)
C6-C5-K1	95.4 (5)
C6-C5-H5	119.3
K1-C5-H5	71.6
C5-C6-H6	119.3
C6-C7-C8	118.2 (7)
C8-C7-C13	118.9 (7)
C10-C8-C7	118.8 (7)
C4-C9-C8	122.4(7)
C8-C9-H9	118.8
C11-C10-H10	119.7
C10-C11-C12	121.3(7)
C12-C11-H11	119.4
O5-C12-C11	114.6(7)
C12-C13-C7	121.3(7)
C7-C13-H13	119.3
O5-C14-H14B	109.5
O5-C14-H14C	109.5
H14B-C14-H14C	109.5

Symmetry transformations used to generate equivalent atoms:
#1 x, y-1, z
#2 x, y+1, z
#3 x-1/2, -y+1/2, -z+1
#4 x+1/2, -y+1/2, -z+1

Crystal Structure Solution from PXRD Data

PXRD data were analyzed using the EXPO Version 2.3.10 software package [56]. The diffraction pattern was indexed using the N-TREOR09 algorithm based on the peaks detected in the 5°–25° 2θ angular range. The triclinic P-1 space group provided the best agreement between the calculated and experimental diffraction data, after several systematic trials. The crystal structure was solved by a simulated annealing approach, involving the generation of random molecular configurations through rotational motions around the molecular center of mass combined with translational movements in all spatial directions. Finally, a full Rietveld refinement was performed to optimize the structural model. CCDC number 2554047 contains the supplementary crystallographic data for this study. These data can be obtained free of charge from the Cambridge Crystallographic Data Center (CCDC) via. www.ccdc.cam.ac.uk/structures".

Table S4. Crystal data and structure refinement for **NP-ANH**

Compound	**NP-ANH**
Empirical formula	$C_{14}\,H_{14}\,K\,O_3$
Formula weight	268.35
Temperature (*K*)	297 (2)
Crystal system	Triclinic
Space group	P-1
a (Å)	14.24(5)
b (Å)	10.34(4)
c (Å)	6.28(2)
α (º)	97.16(16)
β (º)	94.52(19)
γ (º)	72.74(19)
Volume (Å^3)	875(5)
Z	2
Calculated density (g cm^{-3})	1.018
Reflection collected	311
Refinement method	Rietveld
Parameters refined	21
Goodness-on-fit of F^2	12.65561
R	0.33173
CCDC number	2554047

Table S5. Spatial details. Atomic coordinates and equivalent isotropic displacement parameters (Å2) for NP-DH.

	x/a	y/b	z/c	U (eq)
K1	-0.0164	1.3109	1.1506	0.0127
O1	0.4264	0.1544	1.1171	0.0380
O2	0.0685	1.0910	0.8953	0.0380
O3	0.1262	0.9385	1.1266	0.0380
C1	0.3954	0.2853	1.0709	0.0380
C2	0.4320	0.3758	1.2142	0.0380
H1	0.4749	0.3428	1.3264	0.0456
C3	0.4054	0.5121	1.1914	0.0380
H2	0.4308	0.5699	1.2871	0.0456
C4	0.3392	0.5655	1.0230	0.0380
C5	0.3038	0.4748	0.8739	0.0380
C6	0.3331	0.3341	0.9043	0.0380
H3	0.3093	0.2740	0.8091	0.0456
C7	0.3074	0.7059	0.9979	0.0380
H4	0.3293	0.7655	1.0975	0.0456
C8	0.2456	0.7569	0.8325	0.0380
C9	0.2117	0.6637	0.6869	0.0380
H5	0.1687	0.6960	0.5743	0.0456
C10	0.2403	0.5283	0.7068	0.0380
H6	0.2171	0.4701	0.6069	0.0456
C11	0.3804	0.1195	1.2892	0.0380
H7	0.3945	0.0226	1.2829	0.0456
H8	0.3108	0.1588	1.2759	0.0456
H9	0.4049	0.1534	1.4235	0.0456
C12	0.2096	0.9056	0.7996	0.0380
H10	0.1824	0.9128	0.6526	0.0456
C13	0.2896	0.9799	0.8286	0.0380

H11	0.3075	0.9918	0.9782	0.0456
H12	0.2652	1.0670	0.7748	0.0456
H13	0.3460	0.9274	0.7517	0.0456
C14	0.1279	0.9868	0.9521	0.0380

Table S6. Bond lengths [Å] and angles [º] for NP-ANH.

Bond lengths	**Values (E) [Å]**
K1-O2	2.640(10)
K1-C9_a	2.965(11)
O1-C1	1.354(5)
O1-C11	1.441(6)
O2-C14	1.229(5)
O3-C14	1.264(5)
C1-C2	1.401(5)
C1-C6	1.362(5)
C2-C3	1.369(5)
C3-C4	1.411(5)
C4-C5	1.413(5)
C4-C7	1.412(5)
C5-C6	1.423(6)
C5-C10	1.387(5)
C7-C8	1.360(5)
C8-C9	1.409(5)
C8-C12	1.505(6)
C9-C10	1.356(5)
C12-C13	1.540(6)
C12-C14	1.540(6)
C2-H1	0.9200
C3-H2	0.9200
C6-H3	0.9300
C7-H4	0.9200
C9-H5	0.9300
C10-H6	0.9300
C11-H7	0.9600
C11-H8	0.9500

C11-H9	0.9500
C12-H10	0.9800
C13-H11	0.9600
C13-H12	0.9600
C13-H13	0.9500
Bond angle	**Value[º] (E)**
C2-C3-C4	120.61(16)
C3-C4-C5	118.7(2)
C3-C4-C7	122.41(16)
C5-C4-C7	118.9(2)
C4-C5-C6	118.8(2)
C4-C5-C10	118.1(2)
C6-C5-C10	123.16(15)
C1-C6-C5	121.50(16)
C4-C7-C8	122.39(16)
C7-C8-C9	117.2(2)
C7-C8-C12	124.24(15)
C9-C8-C12	118.6(2)
C8-C9-C10	122.0(2)
K1_a-C9-C8	102.5(2)
K1_a-C9-C10	90.2(2)
C5-C10-C9	121.43(16)
C8-C12-C13	114.8(2)
C8-C12-C14	112.56(19)
C13-C12-C14	106.3(2)
O2-C14-O3	124.84(19)
O2-C14-C12	118.5(2)
C4-C7-H4	119.00
C8-C7-H4	119.00

C8-C9-H5	119.00
C10-C9-H5	119.00
K1_a-C9-H5	77.00
C5-C10-H6	119.00
C9-C10-H6	119.00
O1-C11-H7	110.00
O1-C11-H8	110.00
O1-C11-H9	109.00
H7-C11-H8	109.00
H7-C11-H9	109.00
H8-C11-H9	110.00
C8-C12-H10	108.00
C13-C12-H10	107.00
C14-C12-H10	108.00
C12-C13-H11	109.00
C12-C13-H12	110.00
C12-C13-H13	110.00
H11-C13-H12	110.00
H11-C13-H13	110.00

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