Article

Metformin-NSAIDs molecular salts: a path towards enhanced oral bioavailability and stability

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Table of contents

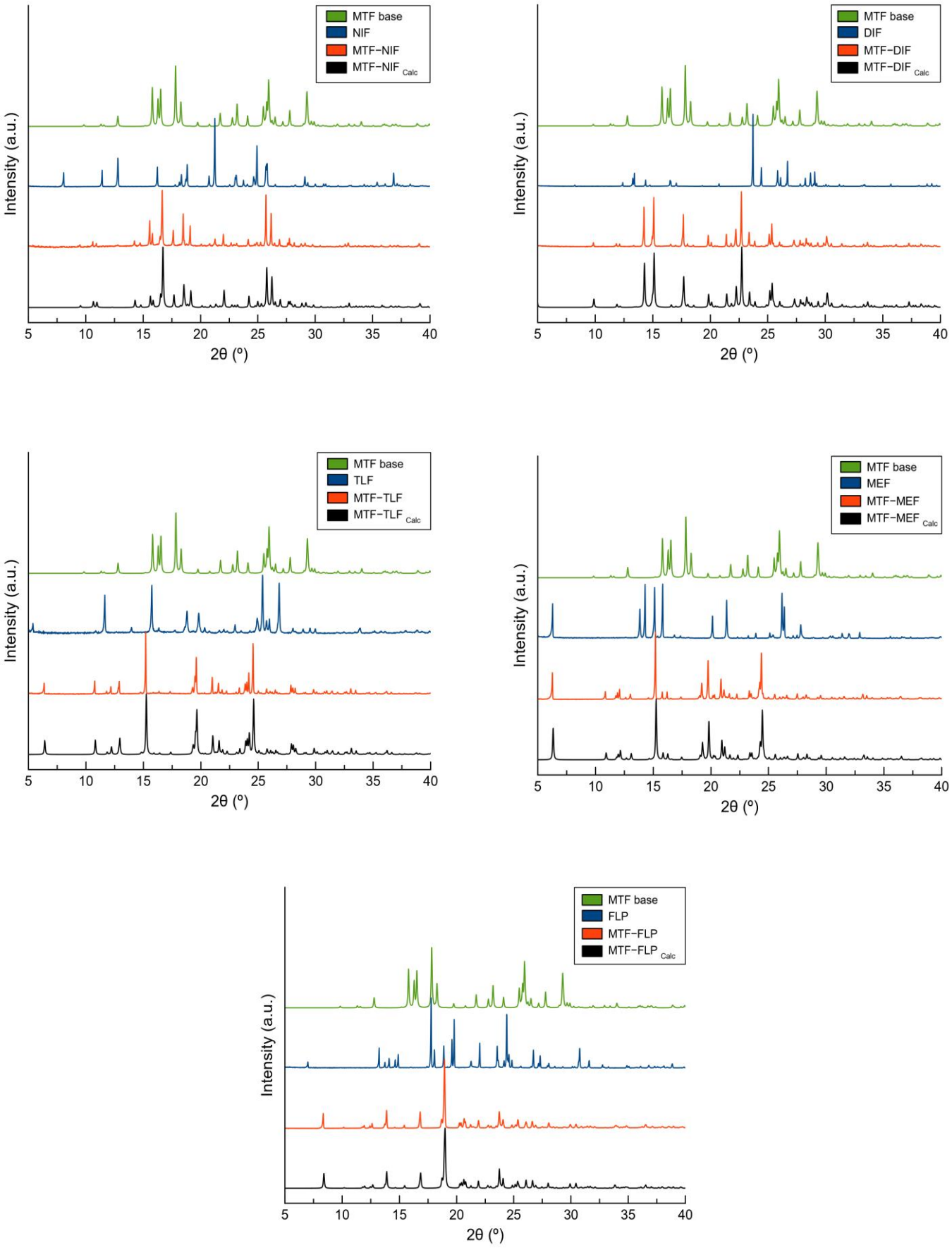

Figure S1. PXRD patterns of the molecular salts obtained by LAG, compared with their respective components.

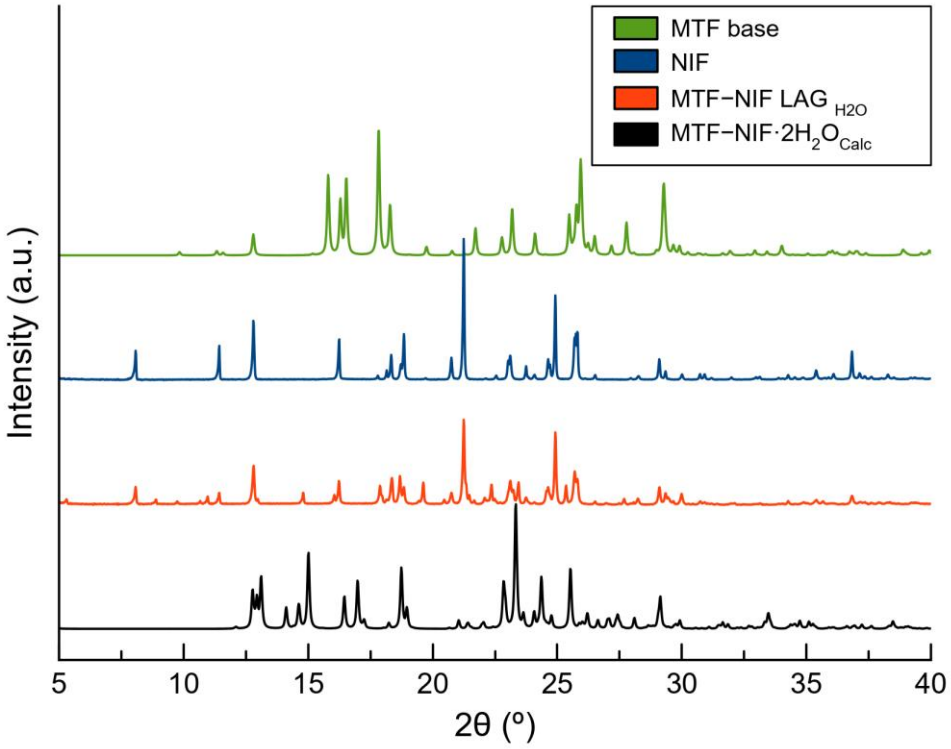

Figure S2. PXRD patterns of MTF–NIF·2H_2O, compared with the product of the LAG in water.

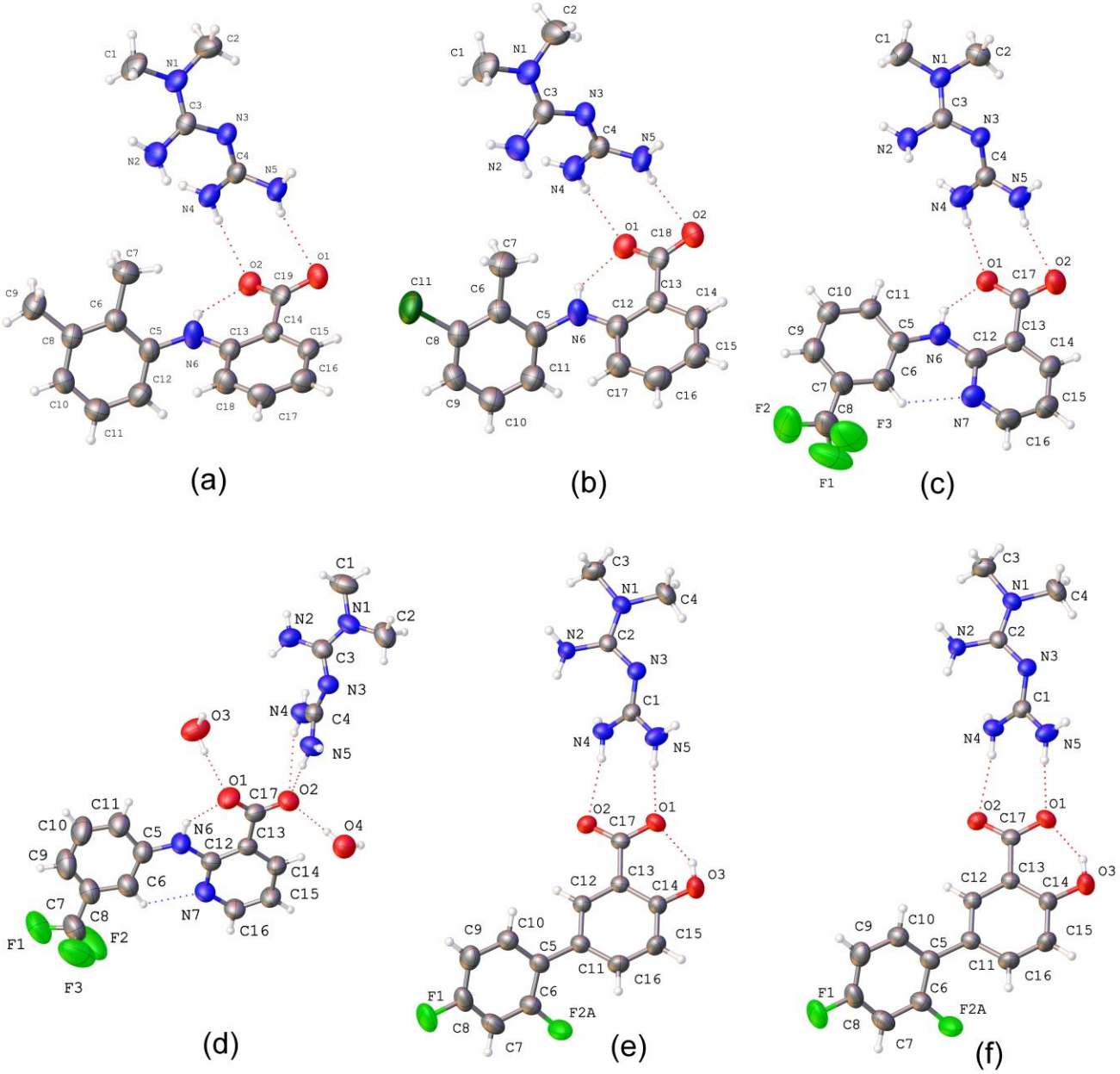

Figure S3. ORTEP representation showing the asymmetric unit of MTF—MEF (a), MTF—TLF (b), MTF—NIF (c), MTF—NIF·2H$_2$O (d), MTF—DIF (e), and MTF—FLP (f) with atom numbering scheme (thermal ellipsoids are plotted with the 50% probability level).

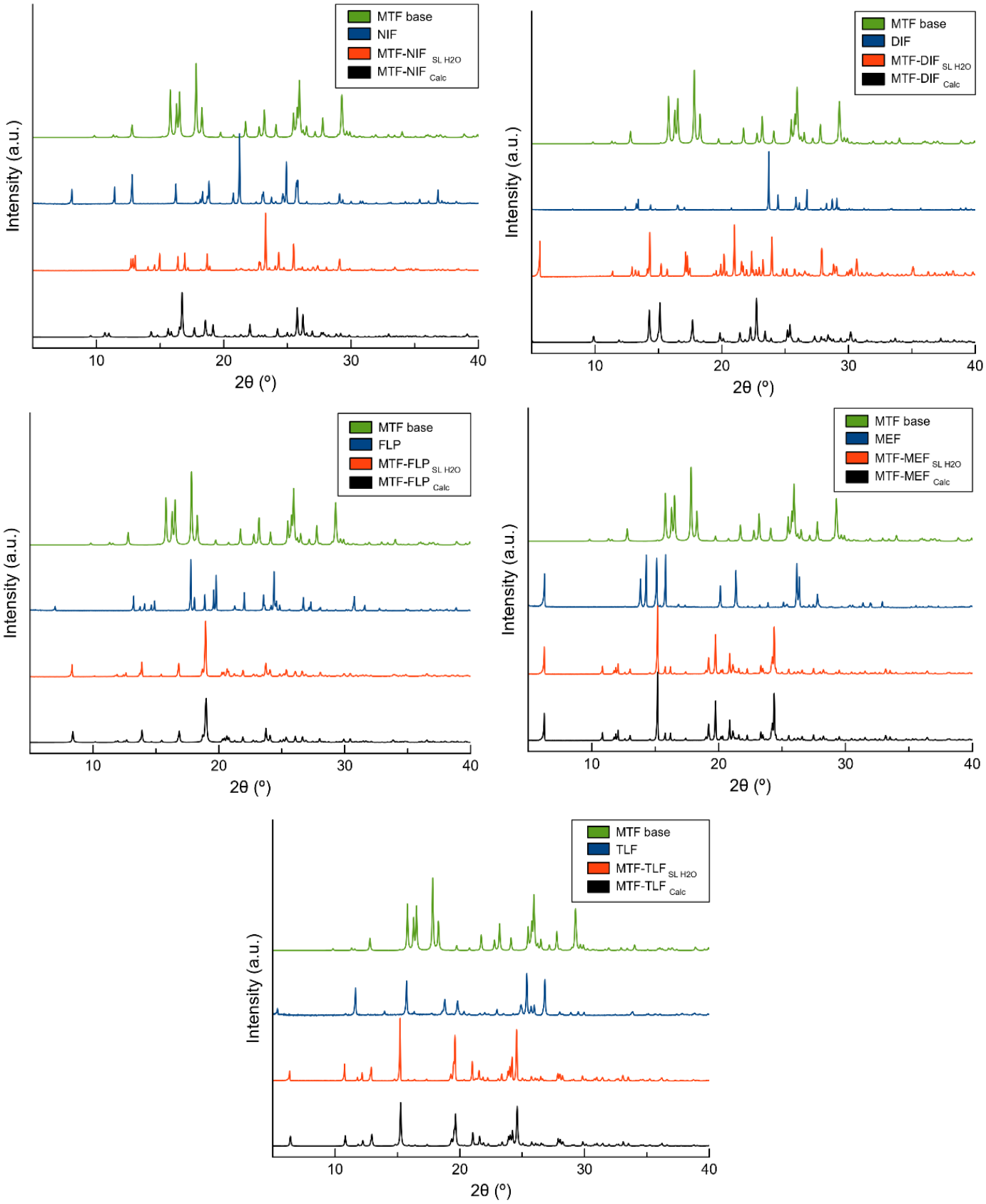

Figure S4. PXRD patterns of the reported molecular salts after aqueous slurrying for 24 hours.

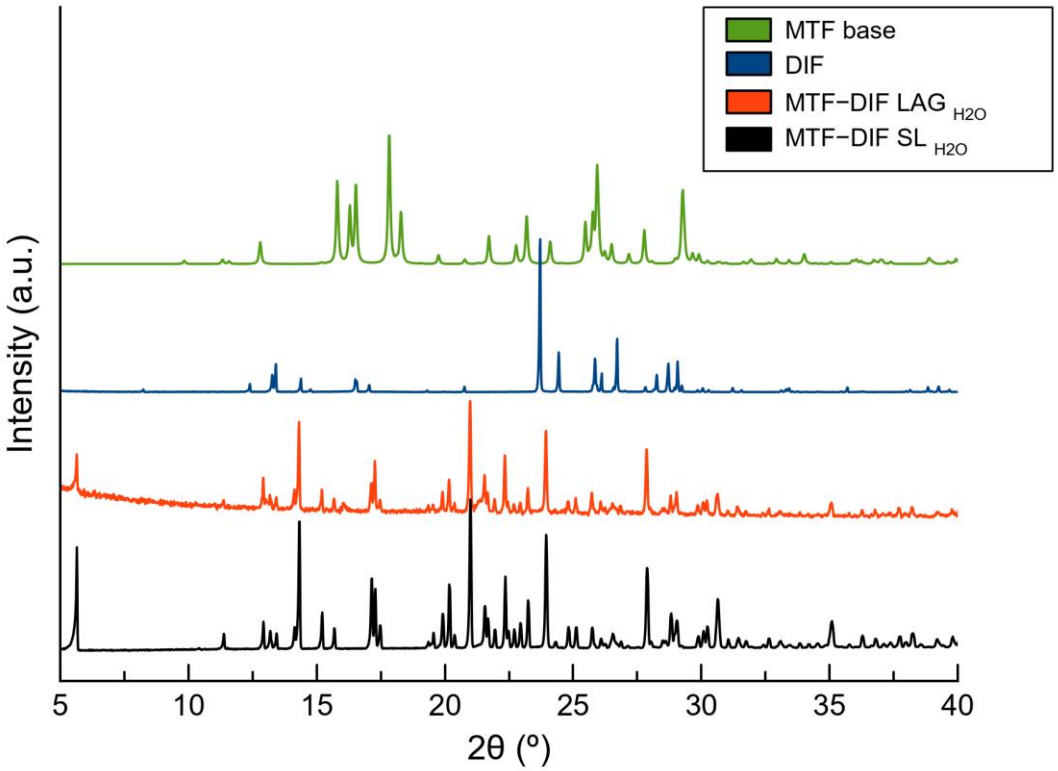

Figure S5. PXRD pattern of LAG of the mixture of MTF and DIF using water as liquid additive compared with the product after the slurry of MTF—DIF in aqueous media.

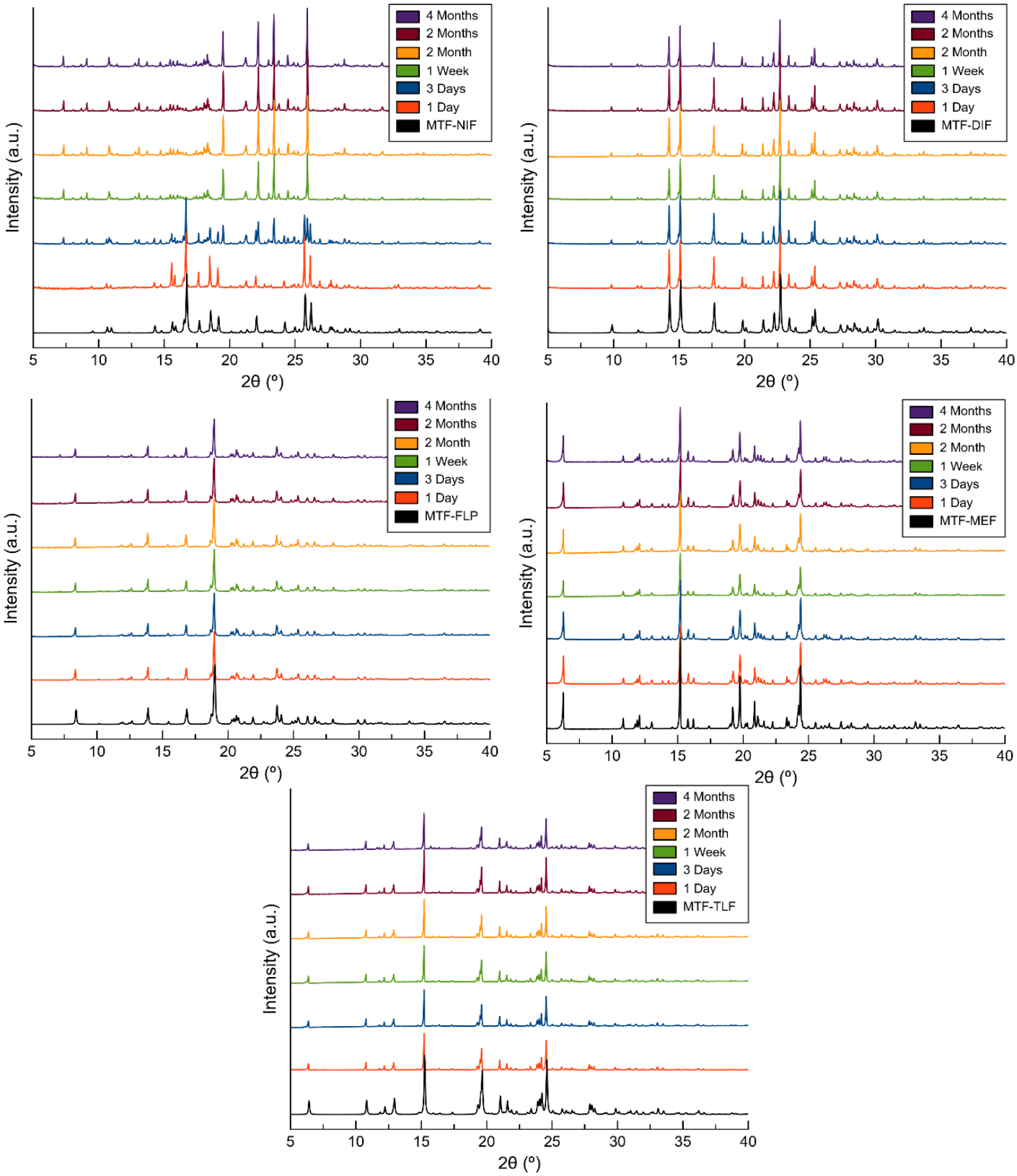

Figure S6. PXRD patterns of reported molecular salts under accelerated ageing conditions for 4 months.

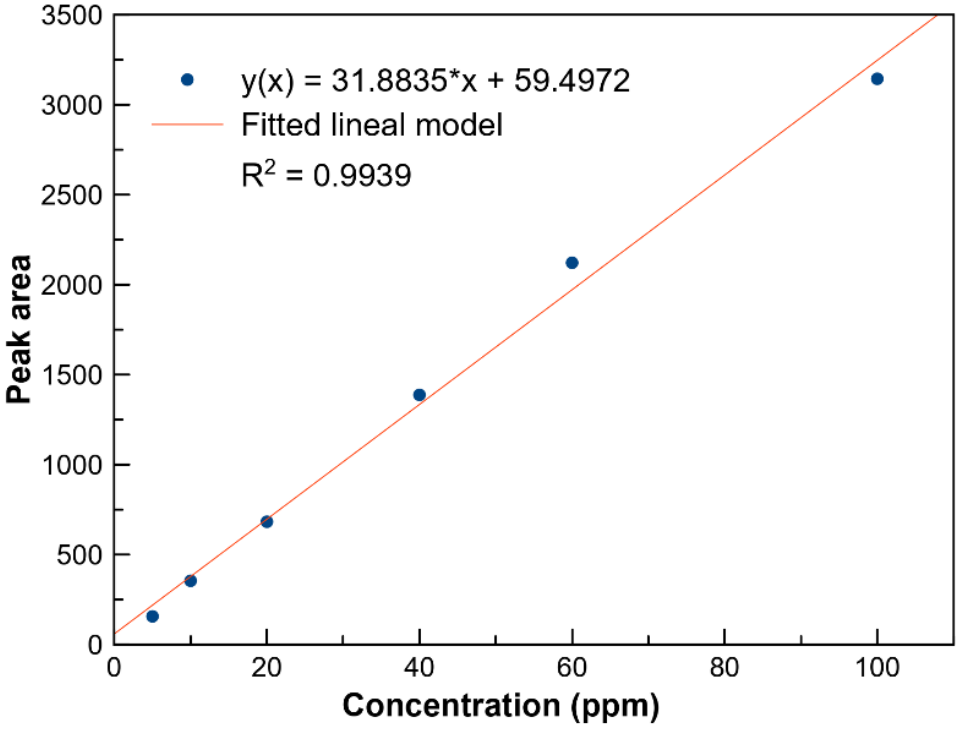

Figure S7. Calibration curve of MTF·HCl determined from HPLC data.

Table S1. HPLC method parameters

Parameter	Details
Column	100 C18 (4.6 mm × 150 mm, 3 μm particle size) Scharlau
Mobile Phase	Isocratic 10% phase A : 90% phase B.
	A= 10% acetonitrile (0.1% Formic acid, v/v) B= 90% water (0.1% Formic acid, v/v).
Flow Rate	1 mL/min
Injected Volume	10 µL
Column Temperature	25 ºC
Sample Temperature	25 ºC
λ_{max}	233 nm
Retention Time	1 minute 54 seconds
Equation	y(x) = 31.8835*x + 59.4972
Regression Coefficient (R^2)	0.9939
Calibration Range	5– 100 mg/L (ppm)

Table S2. Hydrogen bonds for MTF—NSAIDs molecular salts [Å and deg.].

	D-H···A	d(D-H)	d(H···A)	d(D···A)	<(DHA)
MTF-MEF	N(2)-H(2D)···O(1)	0.86	2.17	2.8455(16)	135.4
	N(4)-H(4A)···O(2)#1	0.86	2.15	2.9671(16)	157.9
	N(4)-H(4B)···O(2)#2	0.86	2.11	2.9165(16)	156.1
	N(5)-H(5A)···O(1)#3	0.86	2.11	2.9049(18)	151.8
	N(5)-H(5B)···O(1)#1	0.86	2.23	2.9794(17)	144.9
	N(6)-H(6)···O(2)	0.86	1.96	2.6496(17)	135.7
	#1 x,y+1,z #2 -x+1,y+1/2,-z+3/2 #3 -x+1,-y+2,-z+1				
MTF-TLF	D-H···A	d(D-H)	d(H···A)	d(D···A)	<(DHA)
	N(2)-H(2E)···O(2)	0.86	2.09	2.839(2)	144.9
	N(4)-H(4A)···O(1)#1	0.86	2.16	2.969(2)	157.3
	N(4)-H(4B)···O(1)#2	0.86	2.12	2.930(2)	156.9
	N(5)-H(5A)···O(2)#3	0.86	2.12	2.911(3)	152.0
	N(5)-H(5B)···O(2)#1	0.86	2.16	2.988(2)	161.5
	N(6)-H(6)···O(1)	0.86	1.95	2.637(2)	136.5
	#1 x,y-1,z #2 -x+1,y-1/2,-z+3/2 #3 -x+1,-y,-z+1				
MTF-NIF	D-H···A	d(D-H)	d(H···A)	d(D···A)	<(DHA)
	C(6)-H(6)···N(7)	0.93	2.29	2.883(5)	121.5
	N(2)-H(2D)···N(4)#1	0.86	2.77	3.399(4)	131.1
	N(2)-H(2E)···O(1)#1	0.86	2.60	3.236(4)	131.2
	N(2)-H(2E)···O(2)#1	0.86	2.18	3.035(4)	174.1
	N(4)-H(4A)···O(2)#2	0.86	2.27	3.063(3)	153.3
	N(4)-H(4B)···O(1)	0.86	1.98	2.828(3)	167.6
	N(5)-H(5A)···O(1)#3	0.86	2.14	2.950(3)	156.3
	#1 x-1,y,z #2 x-1/2,-y+1/2,z+1/2 #3 x-1/2,-y+1/2,z-1/2				

Table S2 (cont.). Hydrogen bonds for MTF—NSAIDs molecular salts [Å and deg.].

MTF-NIF·H_2O	D-H···A	d(D-H)	d(H···A)	d(D···A)	<(DHA)
	N(2)-H(2D)···O(3)#1	0.86	2.18	2.923(3)	145.0
	N(2)-H(2E)···O(4)#2	0.86	2.31	3.003(3)	138.3
	N(4)-H(4A)···O(1)	0.86	2.15	2.915(3)	147.2
	N(4)-H(4B)···O(2)#3	0.86	2.43	3.195(3)	148.1
	N(5)-H(5A)···O(3)#4	0.86	2.23	3.032(4)	156.1
	N(5)-H(5B)···O(2)#3	0.86	2.25	3.057(3)	155.6
	C(6)-H(6)···N(7)	0.93	2.30	2.893(4)	120.8
	N(6)-H(6A)···O(1)	0.86	1.91	2.628(3)	139.6
	O(3)-H(3A)···O(1)	0.85	1.90	2.742(3)	170.9
	O(3)-H(3B)···O(4)#5	0.85	1.97	2.816(3)	170.3
	O(4)-H(4C)···O(2)	0.85	1.96	2.808(3)	171.3
	O(4)-H(4D)···O(2)#6	0.85	2.00	2.838(3)	166.4
	#1 x,-y+1/2,z+1/2 #2 -x+2,-y+1,-z+1 #3 -x+2,y+1/2,-z+1/2				
	#4 x,y+1,z #5 x,-y+1/2,z-1/2 #6 -x+2,-y,-z+1				
MTF-DIF	D-H···A	d(D-H)	d(H···A)	d(D···A)	<(DHA)
	N(2)-H(2A)···O(2)	0.86	2.11	2.9209(15)	156.9
	N(2)-H(2B)···N(3)#1	0.86	2.43	3.1618(17)	143.5
	N(4)-H(4E)···O(2)#1	0.86	2.16	3.0116(15)	152.7
	N(5)-H(5A)···O(2)#2	0.86	2.20	3.0505(18)	169.2
	N(5)-H(5B)···O(1)#1	0.86	2.17	2.9569(17)	151.3
	C(15)-H(15)···F(1)#3	0.93	2.57	3.180(2)	123.7
	O(3)-H(3)···O(1)	0.82	1.81	2.5367(15)	146.7
	#1 -x+1/2,y+1/2,-z+1/2 #2 -x+1/2,y-1/2,-z+1/2 #3 x,-y+2,z+1/2				
MTF-FLP	D-H···A	d(D-H)	d(H···A)	d(D···A)	<(DHA)
	N(2)-H(2A)···O(1)#1	0.86	2.11	2.866(2)	146.6
	N(4)-H(4A)···O(2)	0.86	1.95	2.791(3)	165.6
	N(4)-H(4B)···O(2)#2	0.86	2.07	2.861(3)	152.6
	N(5)-H(5A)···O(1)	0.86	2.01	2.867(3)	175.5
	N(5)-H(5B)···N(3)#3	0.86	2.30	3.152(3)	171.3
	#1 x+1,y,z #2 -x+2,-y+1,-z+1 #3 -x+2,-y+1,-z+2				

Table S3. π,π-stacking interactions analysis of compounds MTF—MEF, MTF—TLP and MTF—FLP.

MTF—MEF

```
     6-Membered Ring ( 1)   C5     -->   C6     -->   C8     -->   C10    -->   C11    -->   C12    -->
     6-Membered Ring ( 2)   C13    -->   C14    -->   C15    -->   C16    -->   C17    -->   C18    -->

   Cg(I) Res(I)   Cg(J)  [   ARU(J)]       Cg-Cg Transformed J-Plane P, Q, R, S     Alpha  Beta Gamma    CgI_Perp    CgJ_Perp  Slippage

   Cg1    [ 1] -> Cg1    [  3556.01]  4.0614(11) -0.0357-0.1565-0.9870  -5.2777   0.02(8)  29.3  29.3   3.5431(7)   3.5431(7)   1.985 MEF-MEF
   Cg1    [ 1] -> Cg2    [  4555.01]  5.0184(11)  0.6398 0.6413-0.4236  -8.4282  72.85(8)  25.9  46.9   3.4282(7)   4.5130(6)
   Cg2    [ 1] -> Cg1    [  3566.01]  5.4305(13) -0.0357-0.1565-0.9870  -6.6412  60.29(8)  33.4  86.3   0.3495(6)   4.5334(7)
   Cg2    [ 1] -> Cg1    [  4554.01]  5.0184(11)  0.0357-0.1565 0.9870   1.0898  72.85(8)  46.9  25.9   4.5129(6)   3.4282(7)
                                      ----------                                  ------------------------------------------
                              Min or Max  4.061                                       0.0  25.9  86.3      -3.543      -4.533

   [  3556] = -X,-Y,1-Z
   [  4555] = X,1/2-Y,1/2+Z
   [  3566] = -X,1-Y,1-Z
   [  4554] = X,1/2-Y,-1/2+Z
```

MTF—TLF

```
     6-Membered Ring ( 1)   C5     -->   C6     -->   C8     -->   C9     -->   C10    -->   C11    -->
     6-Membered Ring ( 2)   C12    -->   C13    -->   C14    -->   C15    -->   C16    -->   C17    -->

   Cg(I) Res(I)   Cg(J)  [   ARU(J)]       Cg-Cg Transformed J-Plane P, Q, R, S     Alpha  Beta Gamma    CgI_Perp    CgJ_Perp  Slippage

   Cg1    [ 1] -> Cg1    [  3576.01]  3.9352(16) -0.0211 0.1851-0.9825  -3.6984  0.00(12)  29.4  29.4  3.4277(10)  3.4276(10)   1.933 TLF-TLF
   Cg1    [ 1] -> Cg2    [  4565.01]  5.0454(15)  0.6334-0.6491-0.4212 -14.2733 73.72(12)  28.6  45.1  3.5585(12)  4.4308(10)
   Cg2    [ 1] -> Cg1    [  3566.01]  5.3150(17) -0.0211 0.1851-0.9825  -5.3098 58.63(12)  32.1  89.2  0.0702(10)  4.5011(12)
   Cg2    [ 1] -> Cg1    [  4564.01]  5.0454(15)  0.0211 0.1851 0.9825   2.5195 73.72(12)  45.1  28.6  4.4307(10)  3.5586(12)
                                      ----------                                  ------------------------------------------
                              Min or Max  3.935                                       0.0  28.6  89.2      -3.428      -4.501

   [  3576] = -X,2-Y,1-Z
   [  4565] = X,3/2-Y,1/2+Z
   [  3566] = -X,1-Y,1-Z
   [  4564] = X,3/2-Y,-1/2+Z
```

Table S3 (cont.). π,π-stacking interactions analysis of compounds MTF—MEF, MTF—TLP and MTF—FLP.

MTF—FLP

```
  6-Membered Ring ( 1)   C5     -->   C6     -->   C7     -->   C8     -->   C9     -->   C10    -->
  6-Membered Ring ( 2)   C11    -->   C12    -->   C13    -->   C14    -->   C15    -->   C16    -->


Cg(I) Res(I)   Cg(J)  [   ARU(J)]       Cg-Cg Transformed J-Plane P, Q, R, S     Alpha  Beta Gamma    CgI_Perp    CgJ_Perp  Slippage

Cg1    [ 1] -> Cg1    [  2557.01]    4.015(2) -0.4231-0.2882-0.8590 -10.4389  0.00(16)  17.4  17.4  3.8302(13)  3.8303(13)   1.202 FLP-FLP
Cg1    [ 1] -> Cg2    [  2556.01]  4.9080(18)  0.1215-0.7915-0.5990  -1.3000 46.27(14)  11.4  40.0  3.7580(13)  4.8113(11)
Cg2    [ 1] -> Cg1    [  2556.01]  4.9079(18) -0.4231-0.2882-0.8590  -1.9151 46.27(14)  40.0  11.4  4.8113(11)  3.7579(13)
                                   ----------                                    ---------------------------------------------
                          Min or Max  4.015                                         0.0  11.4  40.0      -4.811      -4.811

[  2557] = -X,-Y,2-Z
[  2556] = -X,-Y,1-Z
```