Drug-drug salt forms of ciprofloxacin with diflunisal and indoprofen

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Experimental Method:

Powder X-Ray Diffraction (PXRD): The PXRD patterns were collected on a Rigaku SmartLab with a Cu Kα radiation (1.540 Å). The tube voltage and amperage were set at 40 kV and 50 mA respectively. Each sample was scanned between 5 and 50° 2θ with a step size of 0.02°. The instrument was previously calibrated using a silicon standard.

Differential Scanning Calorimetry (DSC): DSC was conducted on a Mettler-Toledo DSI1 STAR^e instrument. Accurately weighed samples (4-6 mg) were placed in hermetically sealed aluminium crucibles (40 μL) with a pinhole, and scanned in the range of 30 °C to 300 °C at a heating rate of 5 °C/min under a dry nitrogen atmosphere (flow rate 80 mL/min). The data were managed by STAR^e software.

Thermo gravimetric Analysis: TGA was performed on a Mettler-Toledo TGA/SDTA 851^e instrument. Approximately 6-8 mg of the sample was added to an aluminium crucible and heated from 30 to 450 °C at a rate of 10 °C/min under continuous nitrogen purge.

Host Stage Microscopy: The crystals of CIP/INDP/H_2O were visualized at 20 × magnification and birefringence was observed between crossed polarizer (Olympus optical microscope, model no. BX43) equipped with CCD camera and hot stage). Experiments were performed over a temperature range from 25-300 °C at a heating rate of 5 °C min^{-1}.

FT-IR Spectroscopy (KBr): Fourier transmission infrared spectra of the solids were obtained using a Fourier–transform infrared spectrometer (PerkinElmer 502 or SHIMADZU FTIR-8400S). KBr samples (2 mg in 20 mg of KBr) were prepared and 5 scans were collected at 4 cm-1 resolution for each sample. The spectra were measured over the range of 4000-400 cm^{-1}.

Crystallization: Single crystals were prepared from 50 mg (0.1509 mmol) of CIP and the same equivalents of co-formers, DIF or INDP by dissolving in 10 mL of acetonitrile/methanol mixture and heating the flask until a clear solution was obtained. The good quality single crystals suitable for X-ray diffraction studies were obtained in 3 to 4 days from the slow evaporation method at ambient conditions. We also tried to obtain the single crystals from other common solvents, but did not succeed due to the poor solubility of CIP.

Crystallography: Crystals of CIP salt forms were individually mounted on a glass pip. Intensity data were collected on a Bruker's KAPPA APEX II CCD Duo system with graphite-monochromatic Mo Kα radiation (λ = 0.71073 Å). All the data were collected at r.t. *i.e.*, 298 K. Data reduction was performed using Bruker SAINT software.[1] Crystal structures were solved by direct methods using SHELXL-97 and

refined by full-matrix least-squares on F^2 with anisotropic displacement parameters for non-H atoms using SHELXL-97.[2] Hydrogen atoms associated with carbon atoms were fixed in geometrically constrained positions. Hydrogen atoms associated with oxygen and nitrogen atoms were included in the located positions. Structure graphics shown in the figures were created using the X-Seed software package version 2.0.[2]

Table S1. Geometrical parameters of hydrogen bonds in the salt, CIP/DIF and, salt hydrate, CIP/INDP/H_2O.

CIP/DIF

D—H···A	D···H (Å)	H···A(Å)	D···A (Å)	D—H···A (deg)	Symmetry code
O2–H2···O3	1.00(4)	1.62(4)	2.565(3)	156(4)	X,Y,Z
N3–H3A···O5	0.90	1.81	2.667(3)	159	1+X,Y,Z
N3–H3B···O4	0.90	1.83	2.735(3)	180	1-X,1-Y,1-Z
O6–H6···O5	0.98(4)	1.62(4)	2.523(3)	151(4)	X,Y,Z
C10–H10···F3	0.93	2.44	3.334(5)	160	X,1+Y,1+Z
C12–H12B···O6	0.97	2.36	3.232(4)	150	X,Y,Z
C17–H17A···O3	0.97	2.33	3.301(4)	175	2-X,1-Y,2-Z

CIP/INDP/H_2O

D—H···A	D···H (Å)	H···A(Å)	D···A (Å)	D—H···A (deg)	Symmetry code
O2–H2···O3	0.82	1.74	2.508(3)	155	X,Y,Z
N3–H3A···O5	0.90	1.79	2.684(4)	170	1-X,1-Y,1-Z
N3–H3B···O4	0.90	1.91	2.72	148	1+X,Y,1+Z
O7–H35···O6	0.90(4)	1.96(4)	2.856(4)	172(5)	X,Y,Z
O7–H35A···O1	0.90(5)	1.98(5)	2.867(4)	171(4)	X,1+Y,Z
C14–H14B···O3	0.97	2.21	3.098(4)	151	X-1,Y,Z
C31–H31···O5	0.93	2.42	3.289(5)	155	X-1,Y,Z

Table S2. Rotary evaporator conditions used for the preparation of the salt forms of CIP. The revolution speed (130 rpm) and water bath temperature (50 °C) were always constant. In all the batches 50 mg of

CIP (0.1509 mmol; Sigma-Aldrich) was dissolved in acetonitrile/methanol mixture (20-30 mL) and pressure at rotary evaporator (Büchi) was set to 300 mbar for preparing the solid forms.

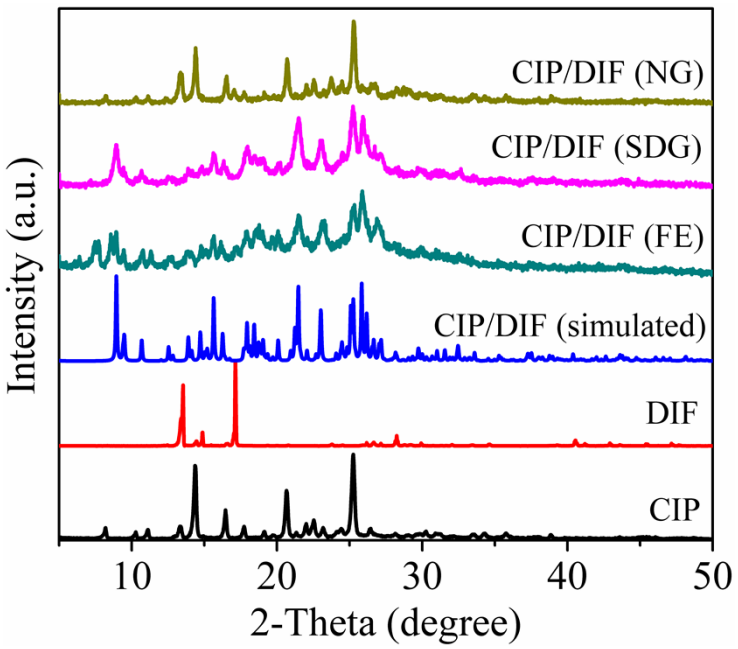
Drug	Co-formers	Weight (mg)	Result	Δ*p*Ka
Ciprofloxacin	Diflunisal	250.2	Formed salt	5.8
	Indoprofen	281.4	Formed salt	2.94
	Pimelic acid	160.2	No co-crystal/salt	4.03
	Glutaric acid	132.1	No co-crystal/salt	4.43
	Adipic acid	146.1	No co-crystal/salt	4.31
	Suberic acid	174.2	No co-crystal/salt	4.22
	Azelaic acid	188.2	No co-crystal/salt	4.19

According to the Δ*p*Ka rule (wherein Δ*p*Ka = *p*Ka (conjugate acid of base) − *p*Ka (acid)), when the Δ*p*Ka is < 3 a neutral co-crystal is expected. When the Δ*p*Ka is > 3 an ionic salt is most likely to form, and the range 0 < ΔpKa < 3 being an unpredictable.[3]

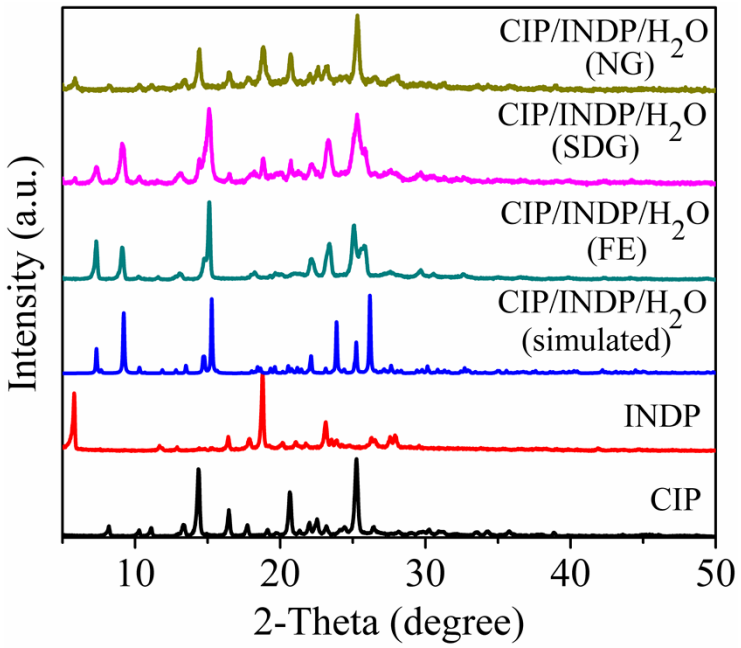
Table S3. Crystallographic data of CIP/DIF and CIP/INDP/H_2O.

	CIP/DIF	CIP/INDP/H_2O
Chemical Formula	C_{30} H_{26} F_3 N_3 O_6	C_{34} H_{35} F N_4 O_7
Formula weight	581.54	630.66
Cryst sys	Triclinic	Triclinic
Space group	*P*-1	*P*-1
a (Å)	7.116(2)	10.325(4)
b (Å)	9.994(4)	12.615(5)
c (Å)	19.147(7)	12.916(5)
α (°)	81.470(9)	71.510(7)
β (°)	82.505(8)	74.334(7)
γ (°)	87.191(8)	70.672(7)
Vol (Å^3)	1334.5(8)	1479.7(10)
D_{calcd} (g/cm^3)	1.447	1.415
μ (mm^{-1})	0.115	0.104
θ range (°)	2.19 - 23.89	2.38 - 23.75
Z	2	2
range *h*	–8 to +8	–12 to +12

range *k*	–11 to +11	–15 to +11
range *l*	–20 to +22	–15 to +15
Reflns collected	14508	16971
Independent reflns	4618	5237
Obsd reflns	2845	2866
T (K)	298	298
*R*1	0.0418	0.0548
*wR*2	0.1122	0.1182
GOF	0.853	1.012
CCDC No.	986495	986496

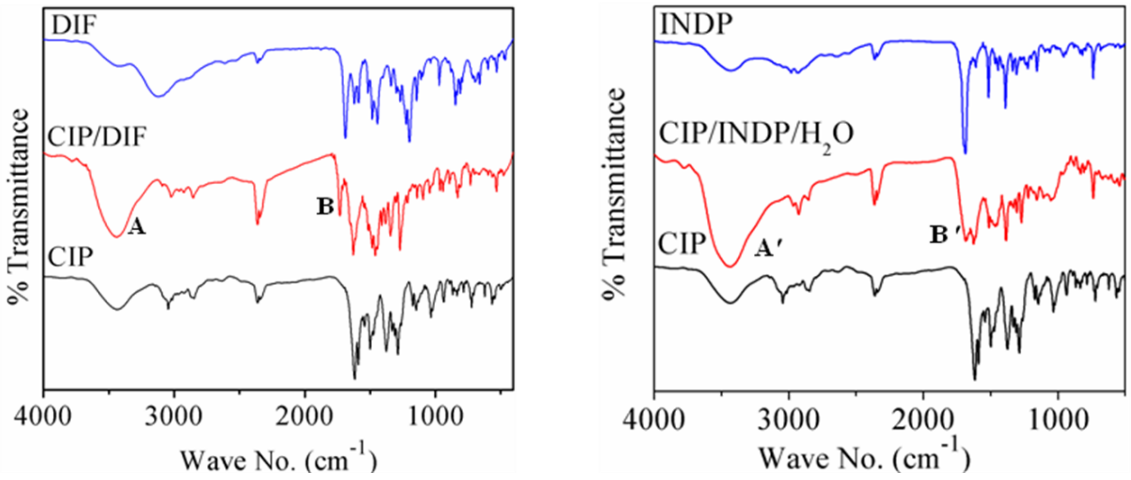


(a)



(b)

Figure S1. Comparison of the PXRD patterns of simulated experimental solid forms. (a) CIP/DIF and (b) CIP/INDP/H_2O. The NG product does not match with simulated PXRD patterns where as LAG and FE product matches. Interestingly the PXRD patterns of CIP/DIF obtained from FE method shows few new peaks which may be due to some unidentified form.



(a) (b)

Figure S2. IR spectra of different forms of ciprofloxacin salts, obtained from using single crystals of sufficient sample size, in each case. (a) CIP/DIF and (b) CIP/INDP/H_2O. In both (a) and (b) peaks A, A′ represent the remarkable intensity increase for 'N-H' stretching frequencies at 3400 and 3439 cm^{-1}

respectively.[4] The observation is mainly because of H-bonding between the CIP and DIF or INDP drugs. The 'C═O' stretching frequency for DIF is 1686 cm^{-1} where as it is 1732 cm^{-1} for CIP/DIF salt which is marked as B in (a), and there is no corresponding change (B′ in (b)) for CIP/INDO/H_2O salt, but a remarkable peak broadening is evident. These changes from individual drugs to salts represent the intermolecular H-bonding between the drugs molecules in the salts.

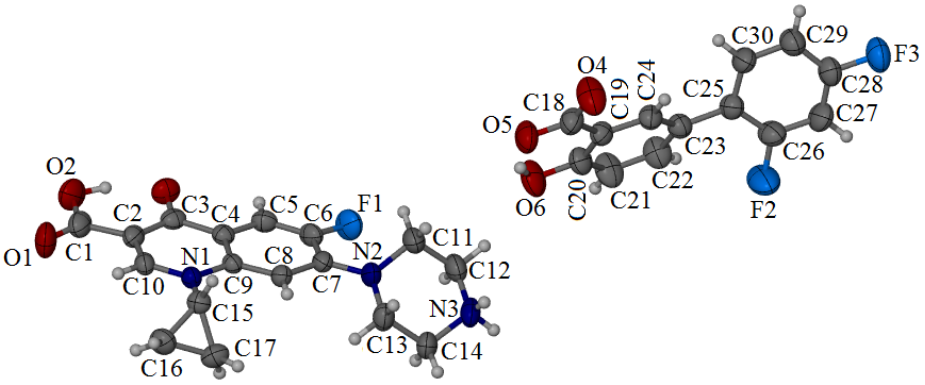


Figure S3. ORTEP diagram of the structure, CIP/DIF. Displacement ellipsoids are drawn at the 50% probability level.

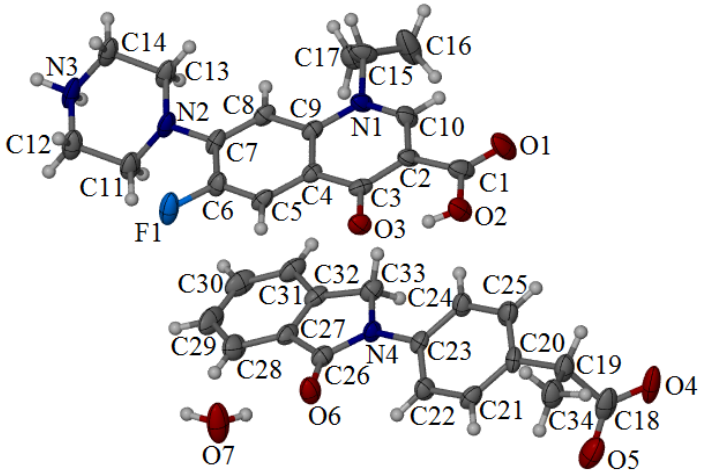


Figure S4. ORTEP diagram of the structure, CIP/INDP/H_2O. Displacement ellipsoids are drawn at the 50% probability level.

References.

1. SAINT Plus (version 6.45), Bruker AXS Inc.: Madison, WI, 2003. (b) SMART (version 5.625) and SHELX-TL (version 6.12), Bruker AXS Inc.: Madison, WI, 2000.

2. L. J. Barbour, X-Seed, Graphical Interface to SHELX-97 and POV-Ray, University of Missouri, Columbia: Columbia, MO, 1999.
3. Palash Sanphui, Geetha Bolla, and Ashwini Nangia, Cryst. *Growth Des*.2012, **12**, 2023.
4. Shaunak Chakraborty, Somnath Ganguly and Gautam R. Desiraju, *CrystEngComm*, DOI:10.1039/c3ce42156b.