Supporting Information For

Mechanical approach for creating different molecular adducts and regulating salt polymorphs: A case study of the anti-inflammatory medication Ensifentrine

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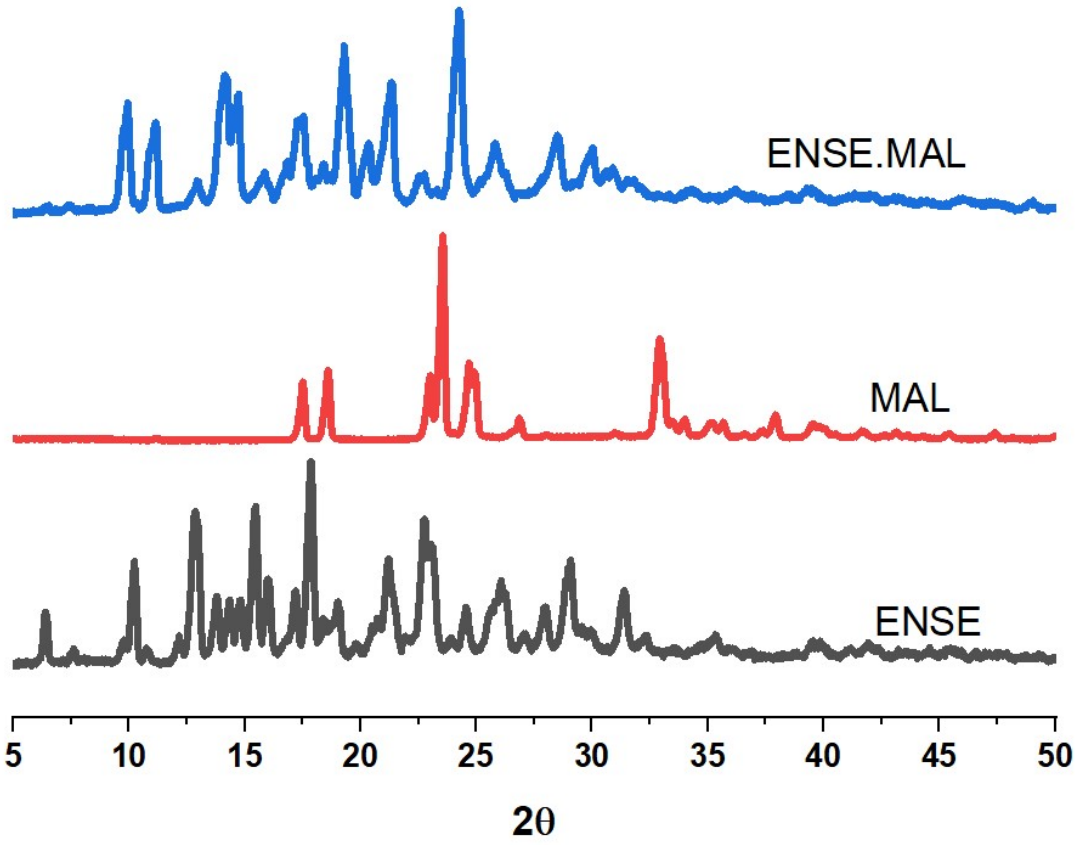
Table S1. p*K*a[a] values of ENSE and salt formers and obtained adducts.

Compound name	p*K*a (acidic medium)	p*K*a (basic medium)	Δp*K*a between ENSE and co-former	Obtained forms
Ensifentrine (ENSE)	14.74	5.23	--------	--------
Malonic Acid (MAL)	4.43	5.41	9.33, 0.80	Salt
Saccharin (SAC)	1.60	1.8	12.94, 3.63	Salt
Succinic Acid	4.2	5.6	9.14, 1.03	Mixture
Glutaric Acid	4.34	5.22	9.52, 0.89	Mixture
Adipic Acid	4.41	5.41	9.33, 0.82	Mixture
Pimelic Acid	4.71	5.58	9.16, 0.52	Mixture
Suberic Acid	4.52	5.49	10.22, 0.71	Mixture
Azelaic Acid	4.55	5.49	9.25, 0.68	Mixture
Fumaric Acid	3.03	4.45	10.29, 2.2	Mixture
L-Malic Acid	3.4	5.2	9.54, 1.83	Mixture
(+)-Tartaric Acid	2.89	4.4	10.34, 2.34	Mixture
Isophthalic Acid	3.46	4.46	10.28, 1.77	Mixture
Terephthalic Acid	3.54	4.34	10.4, 1.69	Mixture
3-Hydroxybenzoic acid(3-HBA)	3.84	6.1	8.64, 1.39	Mixture
Phthalic Acid	2.89	5.51	9.23, 2.34	Salt
Salicylic Acid	2.79	6.3	8.44, 2.44	Salt
4-Hydroxybenzoic acid(4-HBA)	4.58	9.49	5.25, 0.65	Mixture
2,4-Dihydroxybenzoic acid (2,4-DHBA)	3.1	5.8	8.94, 2.13	Mixture
2,5-Dihdroxybenzoic acid	2.97	5.9	8.84, 2.26	Mixture

[a]pKa values were determined using Marvin 5.10.1, 2012, ChemAxon, http://www.chemaxon.com. These values are closely resembling with pKa values compiled by R. Williams.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MAL
ENSE
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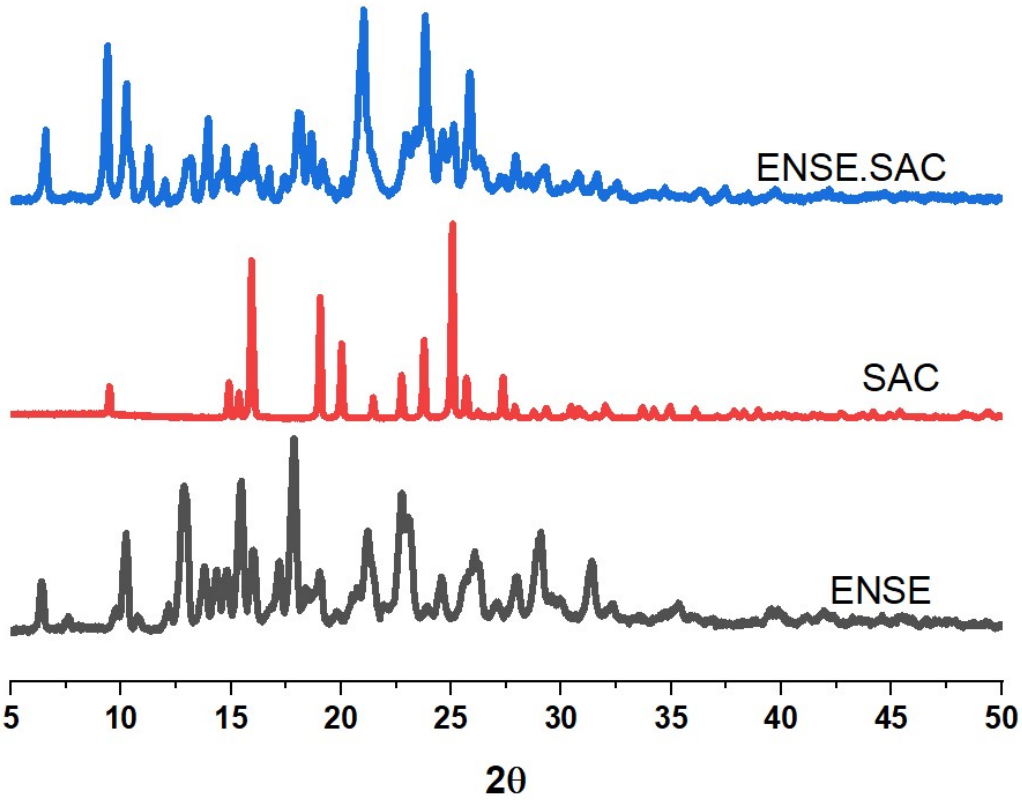
2θ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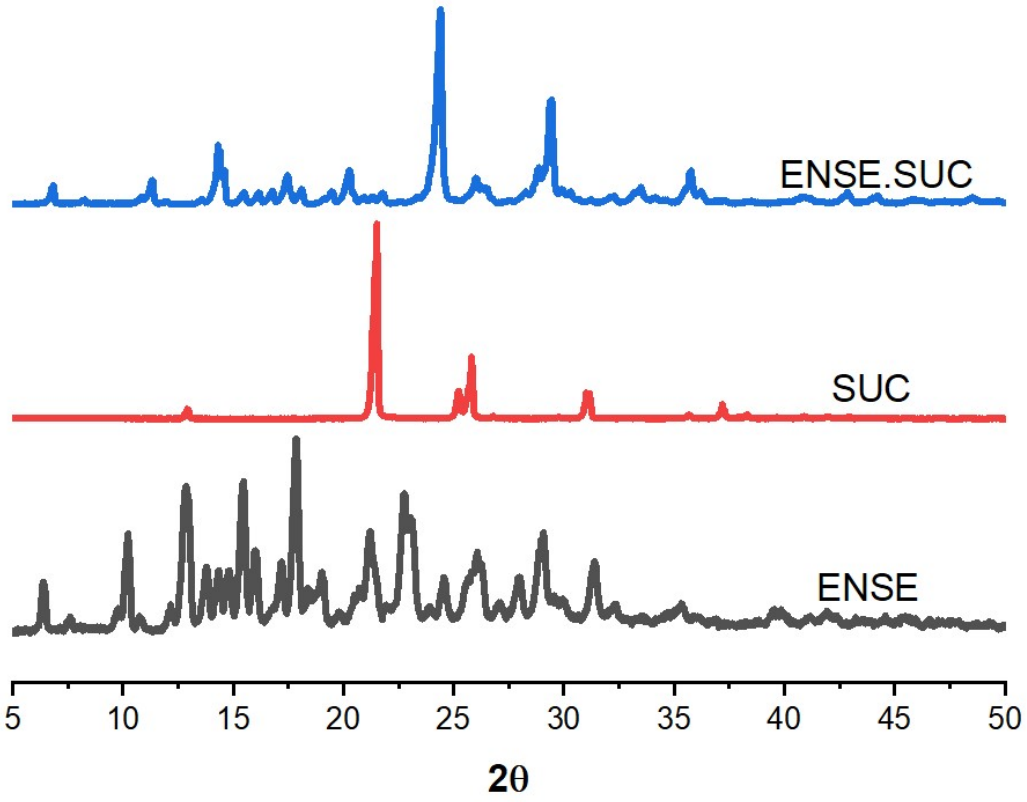
2θ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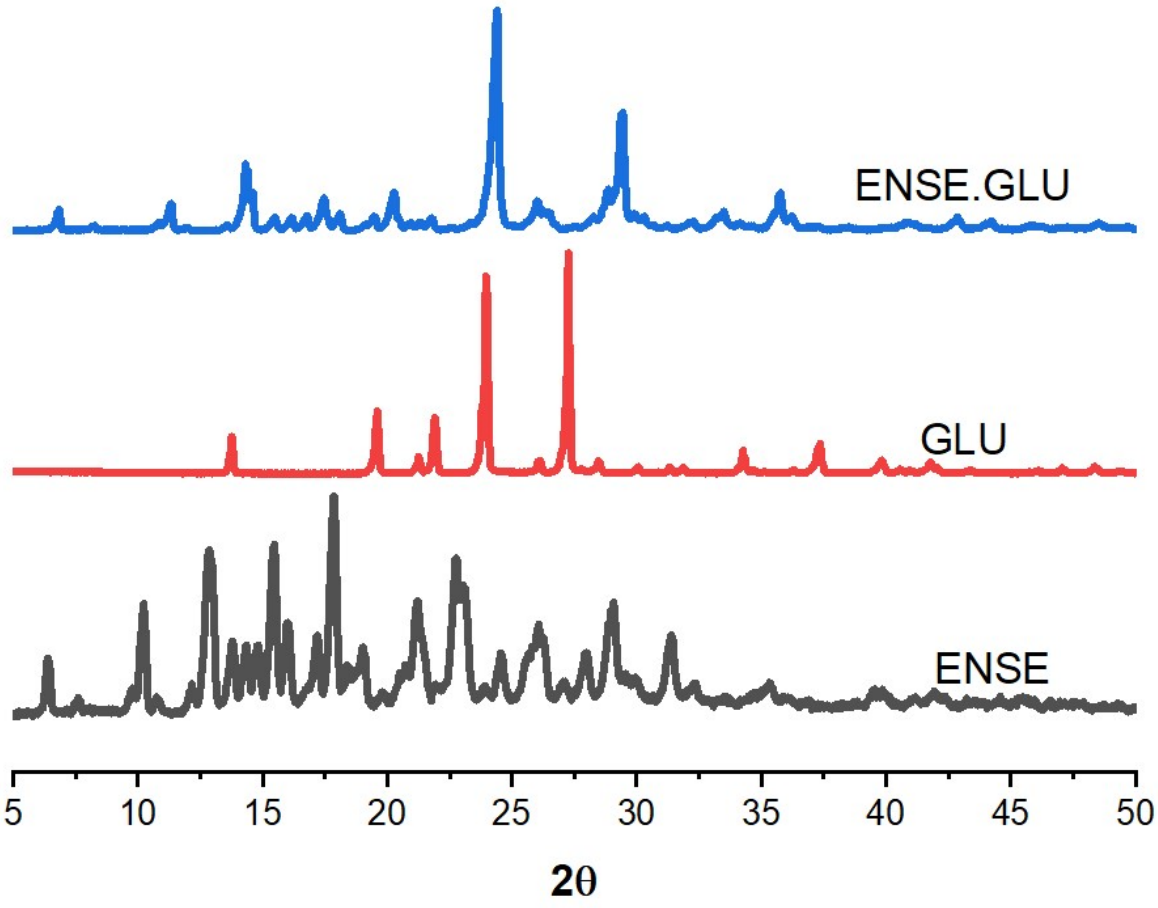
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GLU
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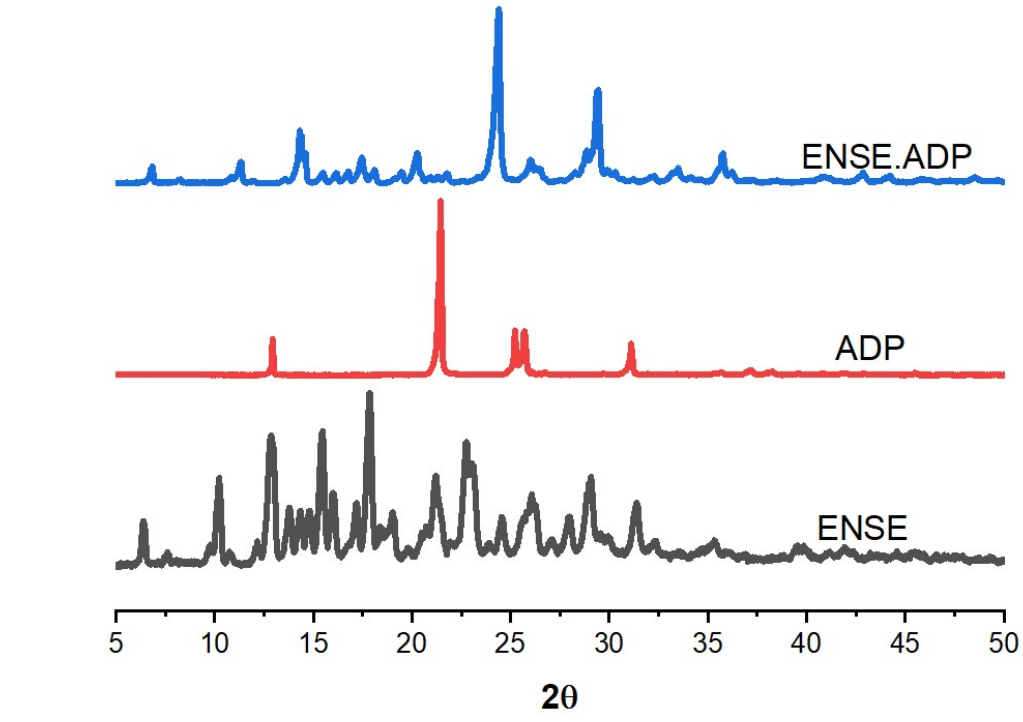
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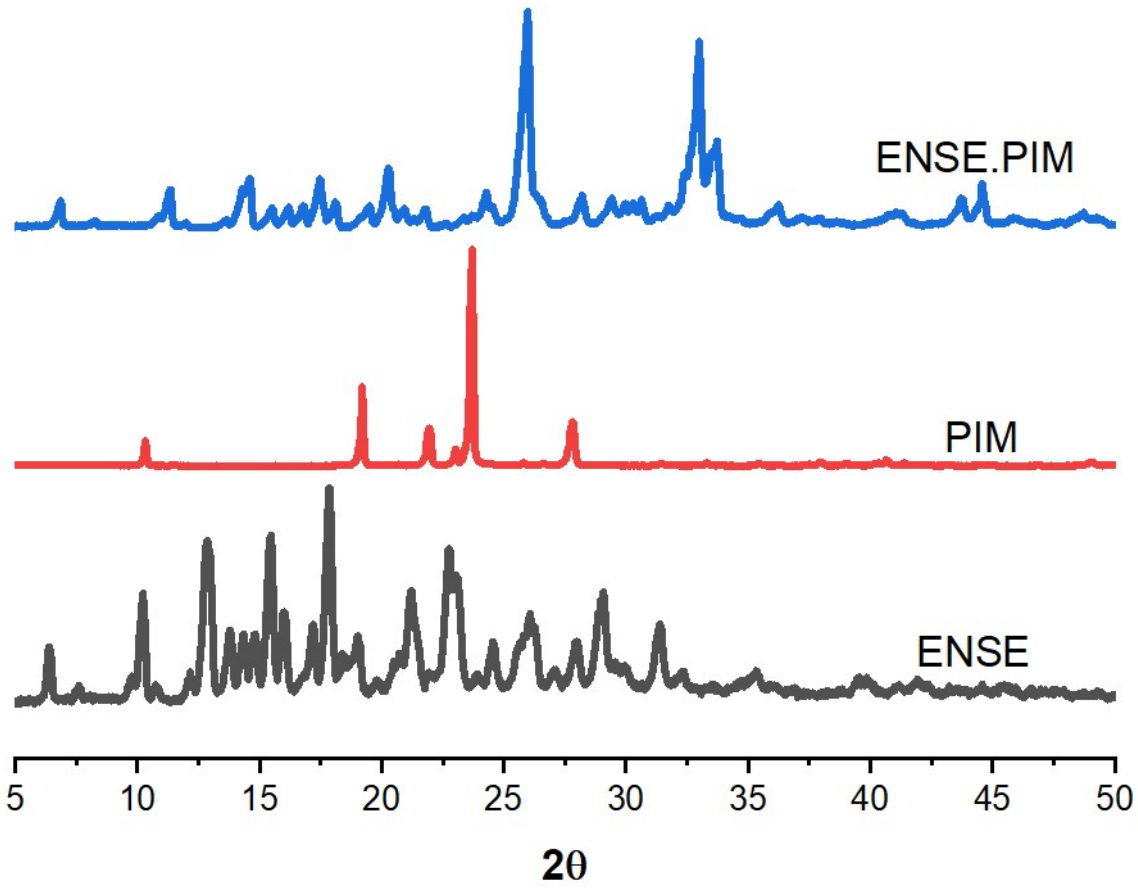
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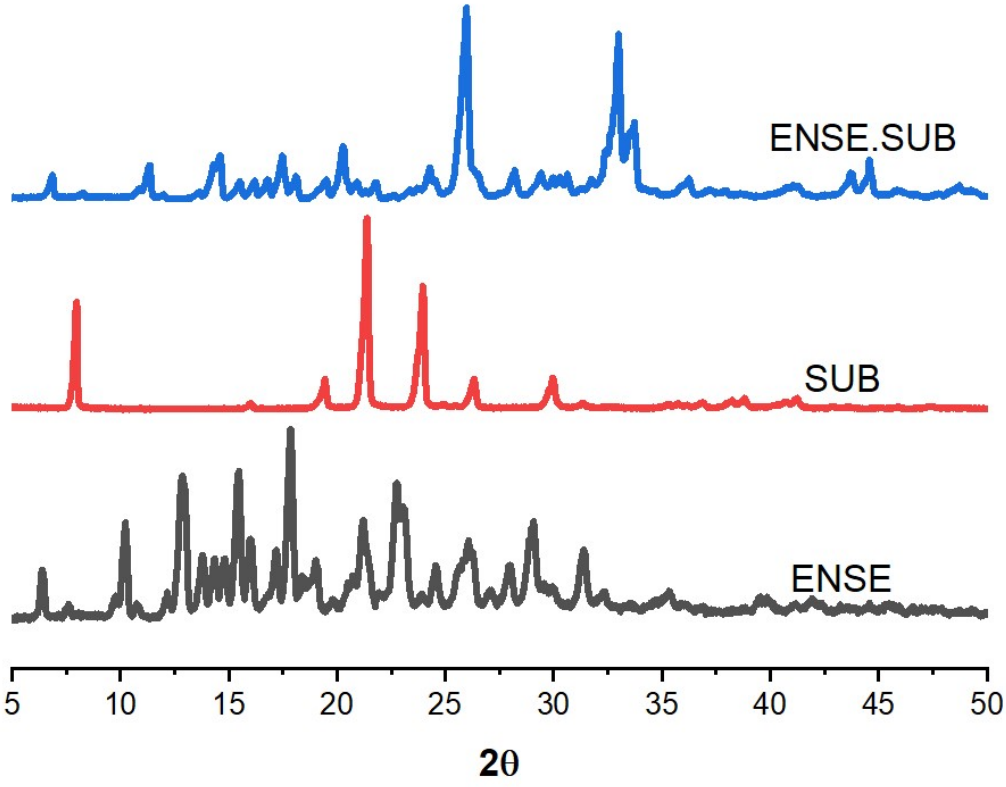
2θ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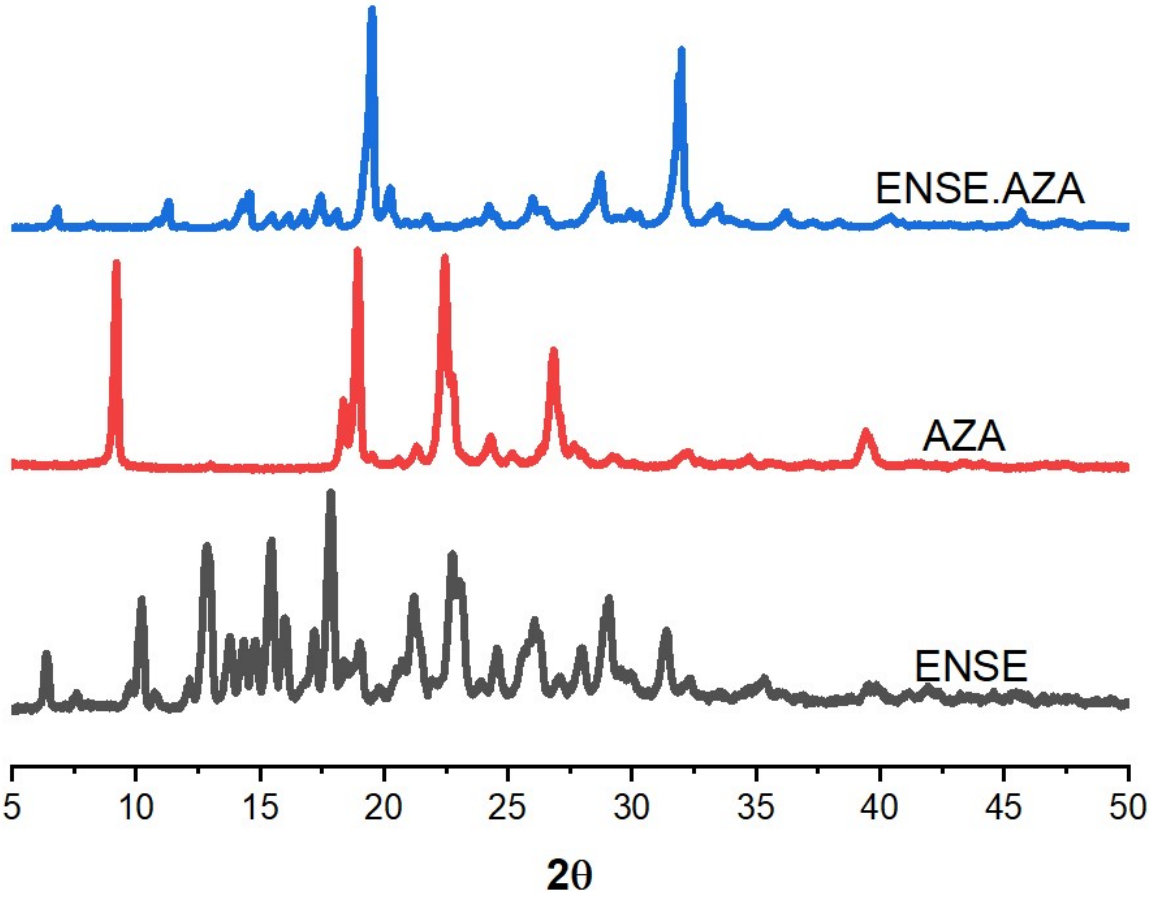
2θ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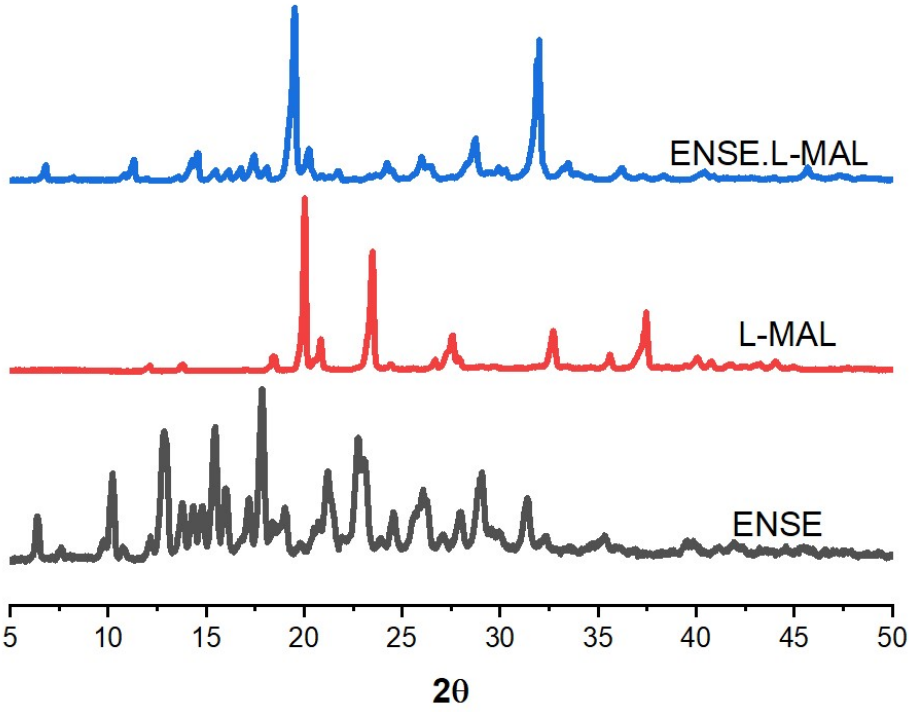
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L-MAL
ENSE
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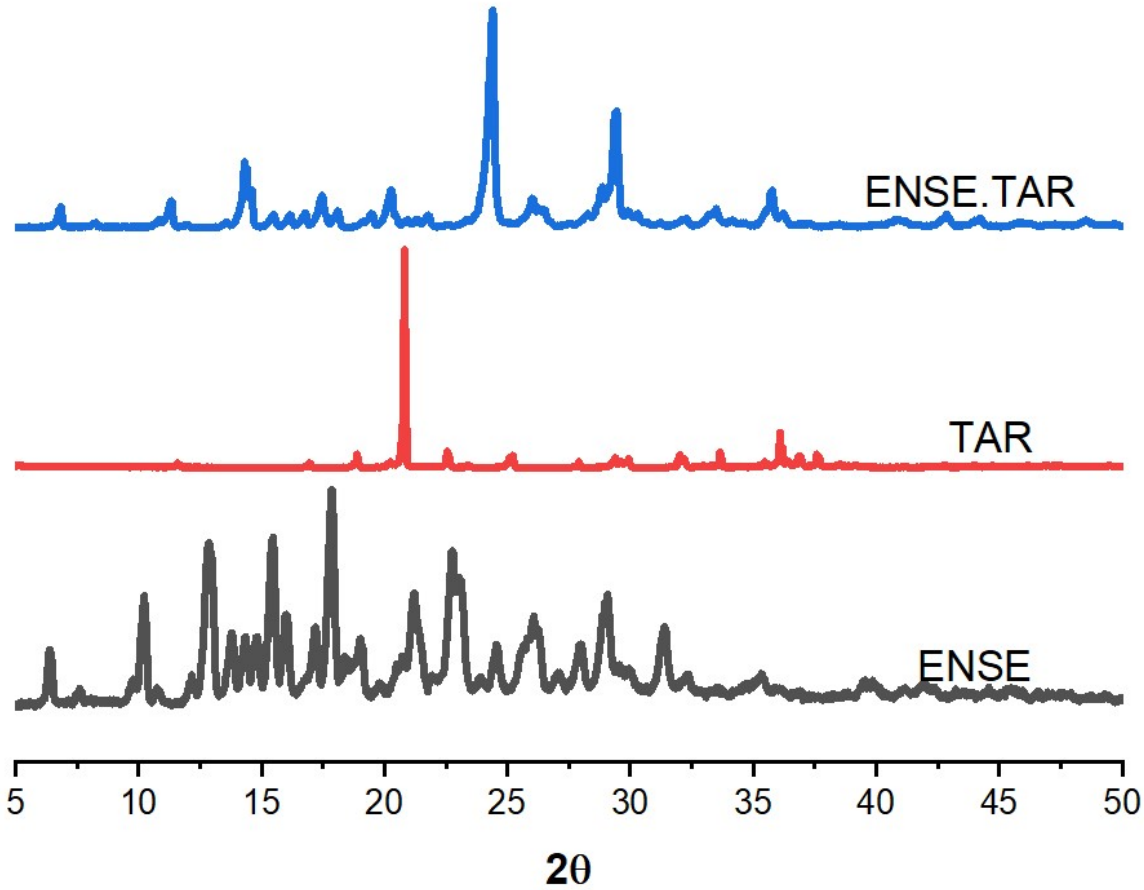
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TAR
ENSE
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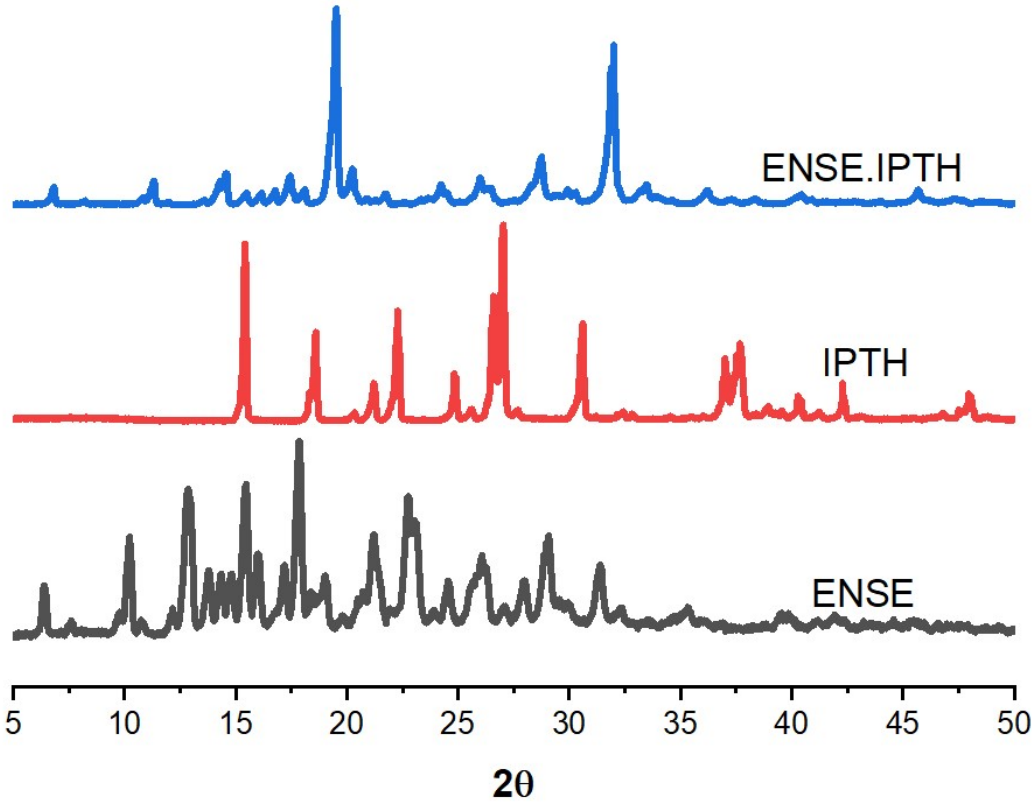
2θ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IPTH
ENSE
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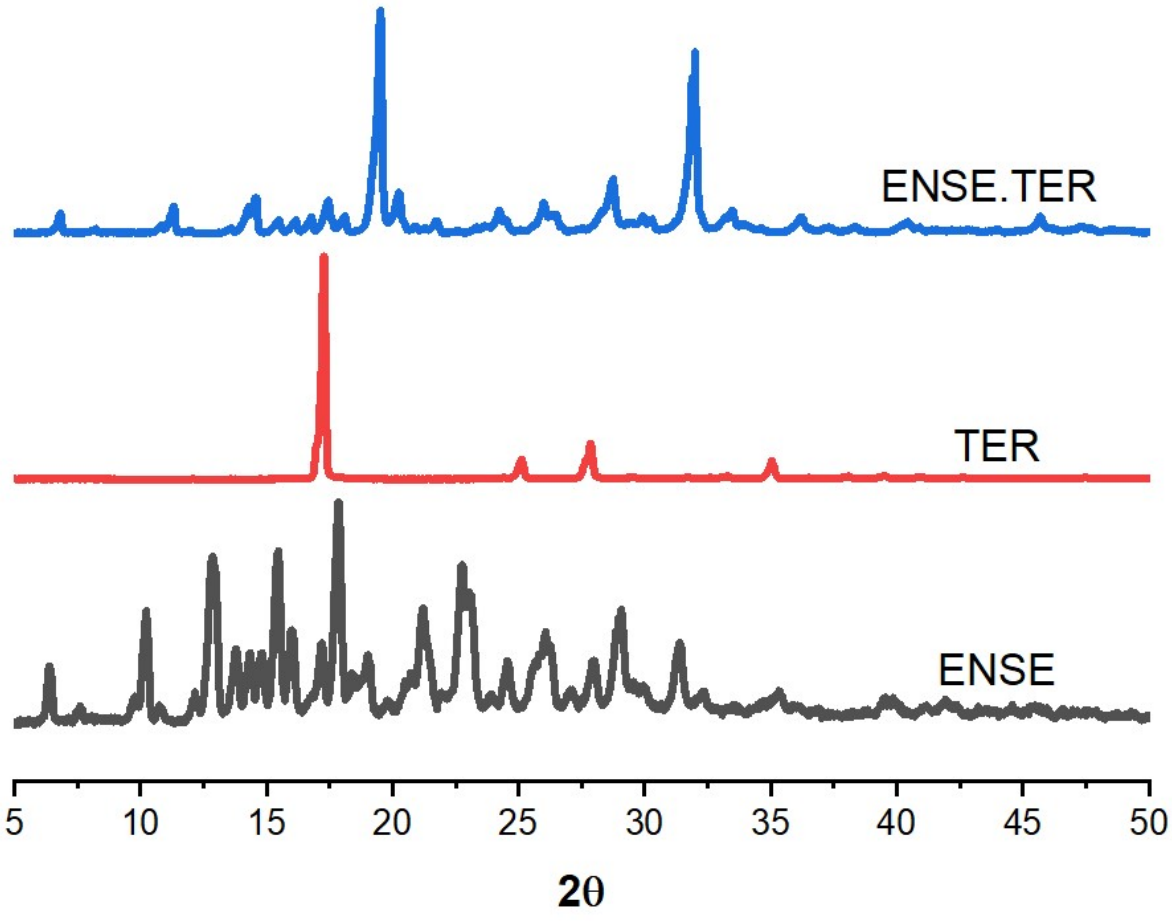
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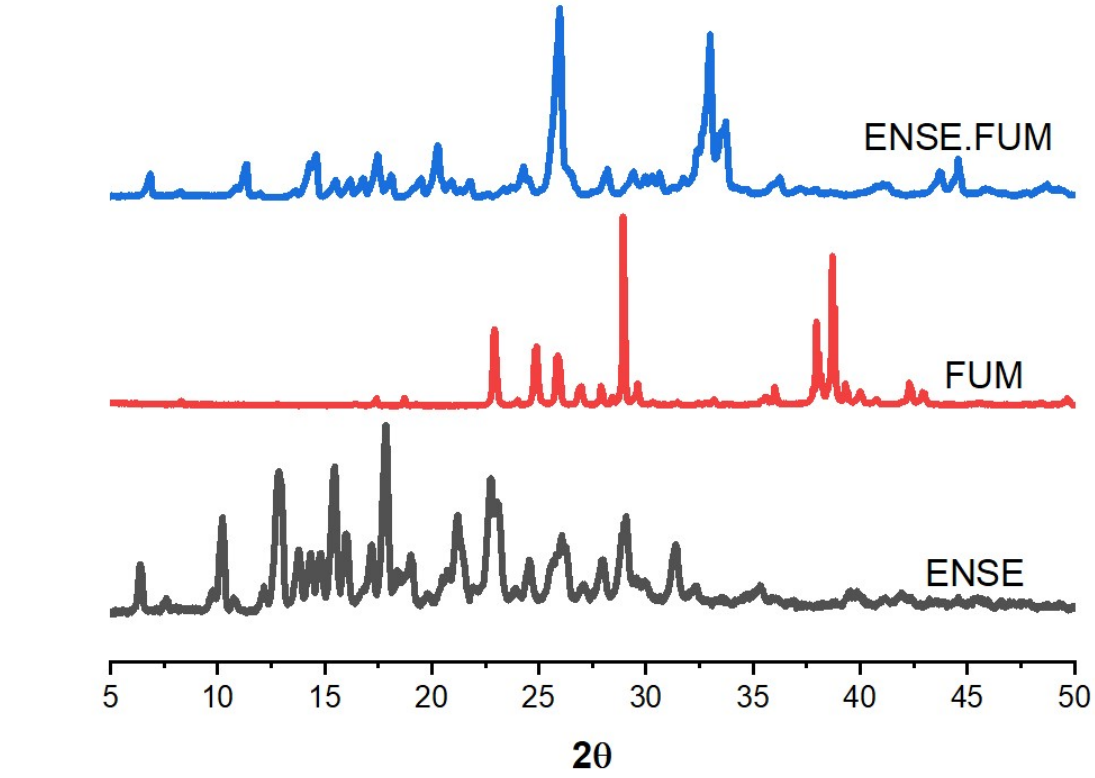
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FUM
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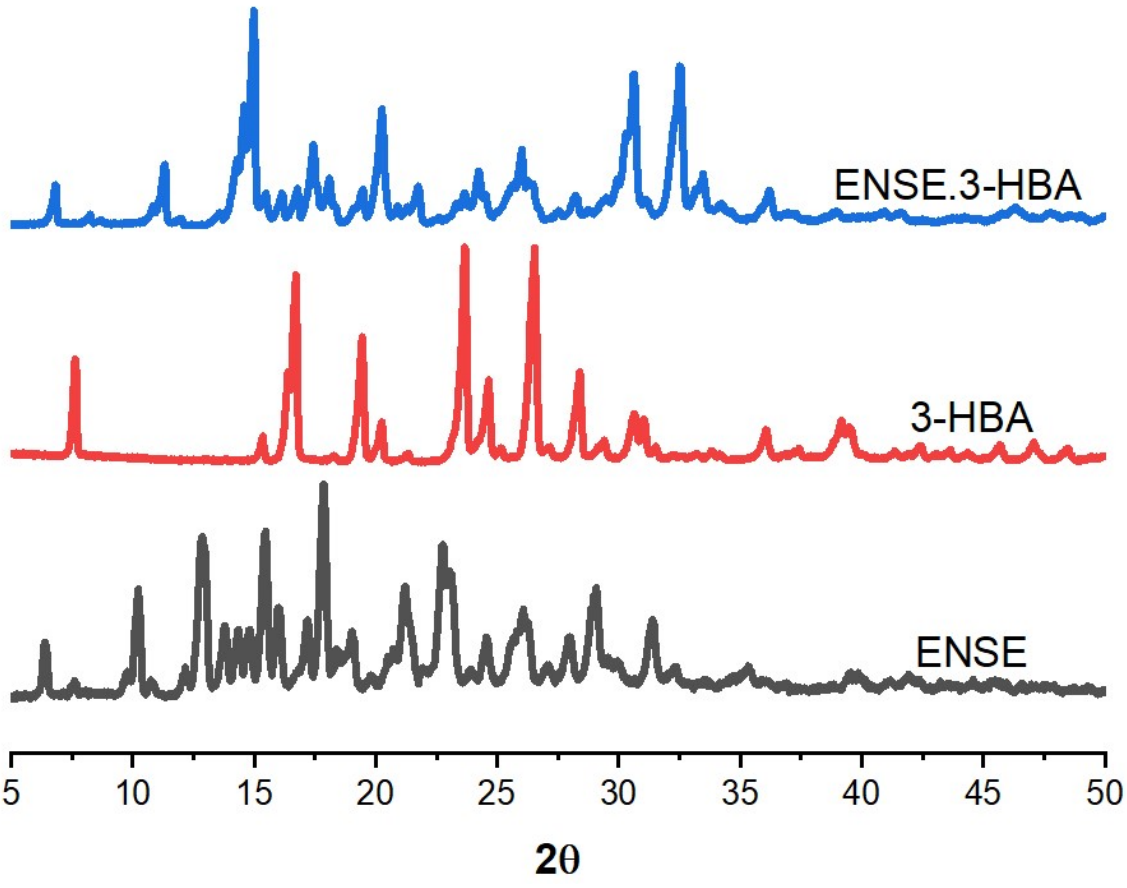
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3-HBA
ENSE
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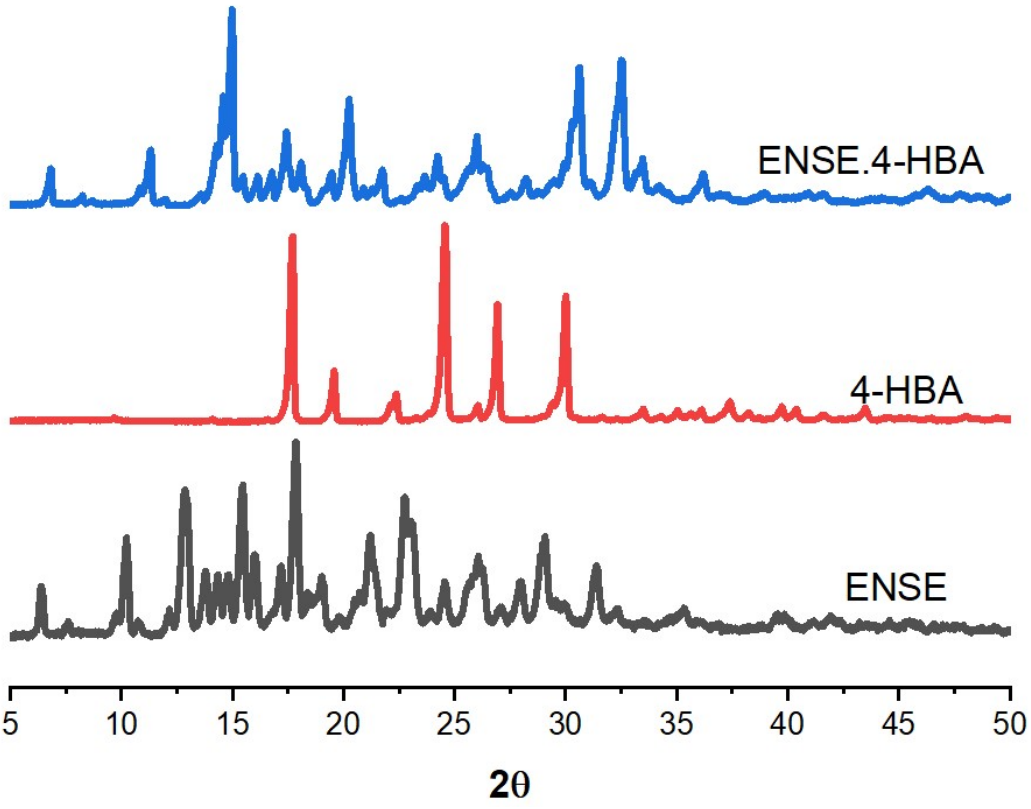
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4-HBA
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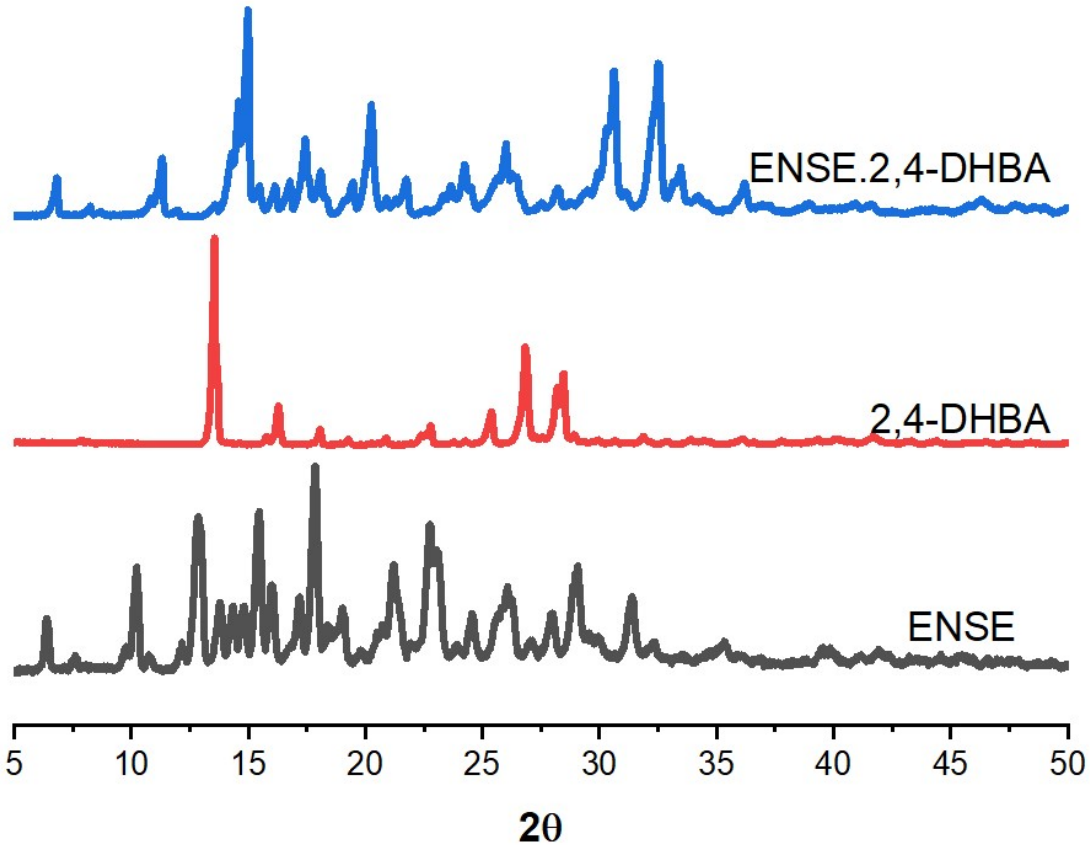
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2,4-DHBA
ENSE
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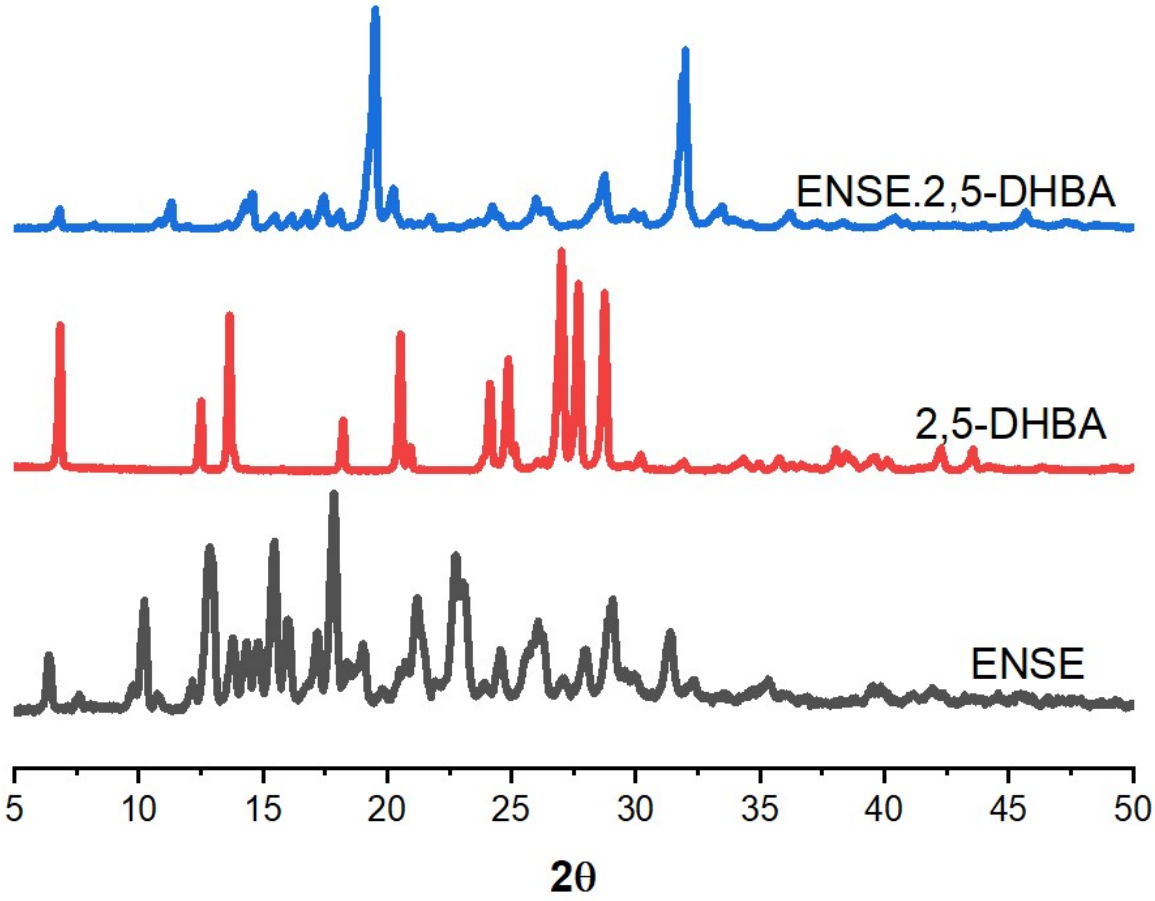


Figure S1. PXRD screening method to evaluate the probable production of binary adducts between ENSE and GRAS co-former.

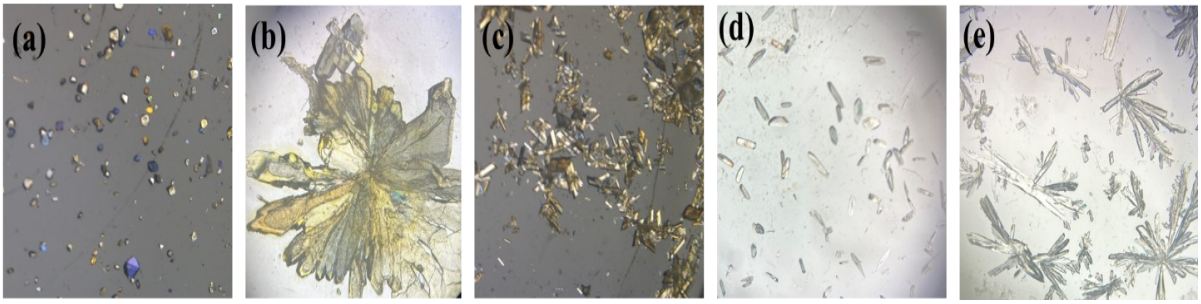


Figure S2. Optical microscopic images of different solid forms of ENSE.

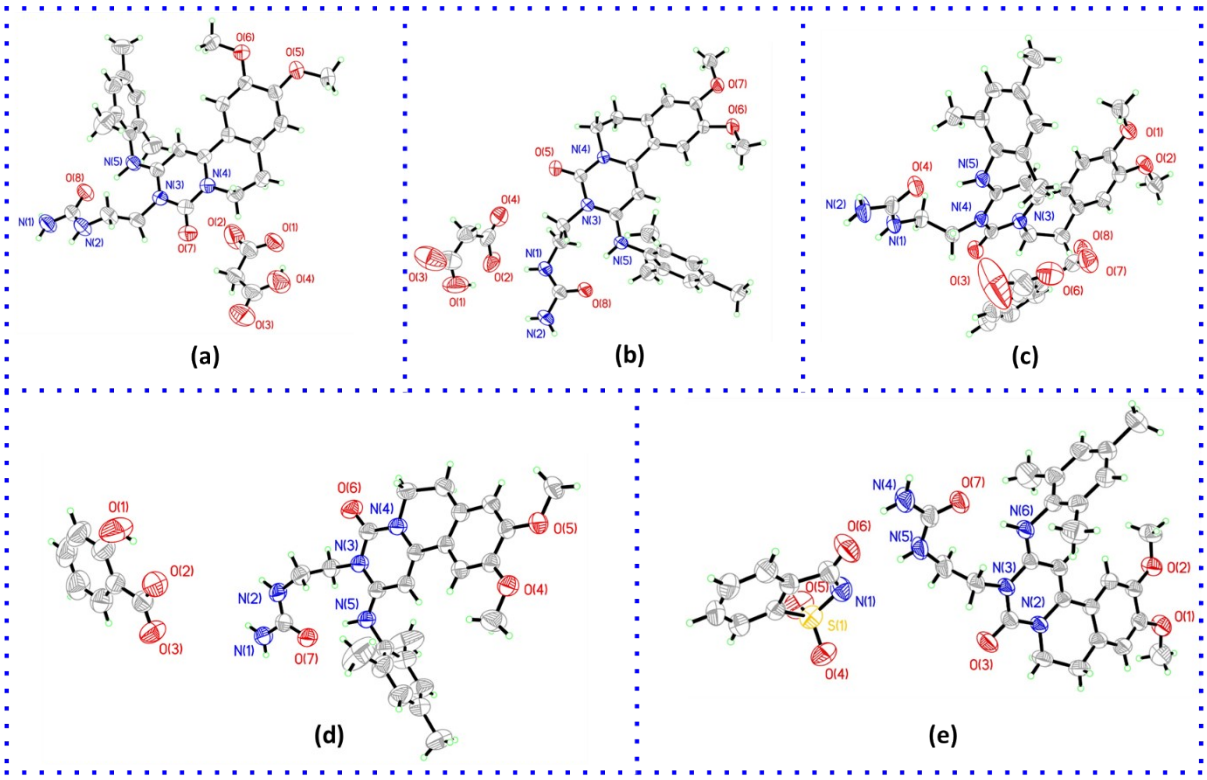


Figure S3. ORTEP view of (a) ENSE.MAL(α), (b) ENSE.MAL(β), (c) ENSE.PTH (d) ENSE.SAL and (e) ENSE.SAC. Herein, the ellipsoids are drawn with a 50% probability.

Table S2. Hydrogen bond distances (Å) and angles (°) of molecular adducts of ENSE.

Solid forms	*D*–H···*A*	*D*–H(Å)	H···*A*(Å)	*D*–*A*(Å)	*D*–H···*A*(°)
ENSE.MAL(α)	O4−H4···O1^{-}(Intra)	0.820	1.69	2.451(1)	154
	N2−H100···O1^{-}	0.890	2.01	2.902(1)	174
	N1−H1B···O2	0.860	2.06	2.901(2)	166
	N1−H1A···O2	0.860	2.21	2.982(1)	149
	N5^{+}−H103···O8(Intra)	1.040	1.65	2.673(1)	165
	C15−H15···O3	0.930	2.30	3.231(1)	172
	C9−H101···O2	0.962	2.42	3.261(2)	148
ENSE.MAL(β)	O1−H6···O2^{-}(Intra)	0.820	1.88	2.456(1)	126
	N4^{+}−H5···O8(Intra)	0.905	1.86	2.749(1)	164
	N2−H2A···O4	0.860	2.05	2.912(2)	176
	N2−H2B···O5	0.860	2.50	3.117(1)	129
	N1−H2···O2^{-}	0.935	1.98	2.903(1)	166
	C7−H7A···O2^{-}	0.970	2.57	3.377(1)	144
ENSE.PTH	N2−H2A···O3	0.860	2.26	3.111(1)	167
	N5^{+}−H80···O4(Intra)	0.950	1.84	2.785(2)	169
	N1−H1A···O8	0.860	2.18	3.020(1)	164

	N2−H2B···O7^{-}	0.860	2.12	2.900(1)	150
	C17−H17A···O4	0.960	2.71	3.111(1)	143
	C1−H1A···O5	0.960	2.19	3.125(1)	164
	C31−H31···O4	0.930	2.54	3.324(1)	142
	C–H2E···O2	0.960	2.57	3.431(2)	149
ENSE.SAL	O1−H103···O2(Intra)	0.819	1.76	2.493(1)	148
	N2−H102···O2^{-}	0.906	2.04	2.997(1)	176
	N1−H1B···O3	0.860	1.99	2.828(2)	164
	N5^{+}−H80···O7(Intra)	0.961	1.76	2.719(3)	170
	N1−H1A···O3	0.860	2.20	2.917(1)	139
	C19−H19B···O4	0.970	2.47	3.263(1)	139
	C3−H3···O7	0.930	2.90	3.783(2)	158
ENSE.SAC	N1−H71···N5^{-}	0.858	2.44	3.294(2)	169
	N4−H4A···O6	0.860	2.25	2.876(1)	129
	N4−H4B···O6	0.860	2.02	2.839(2)	157
	N6^{+}−H80···O7(Intra)	0.907	1.91	2.804(2)	167
	C15−H15B···O2	0.970	2.40	3.252(3)	146
	C27−H33···O7	0.930	2.62	3.532(1)	165

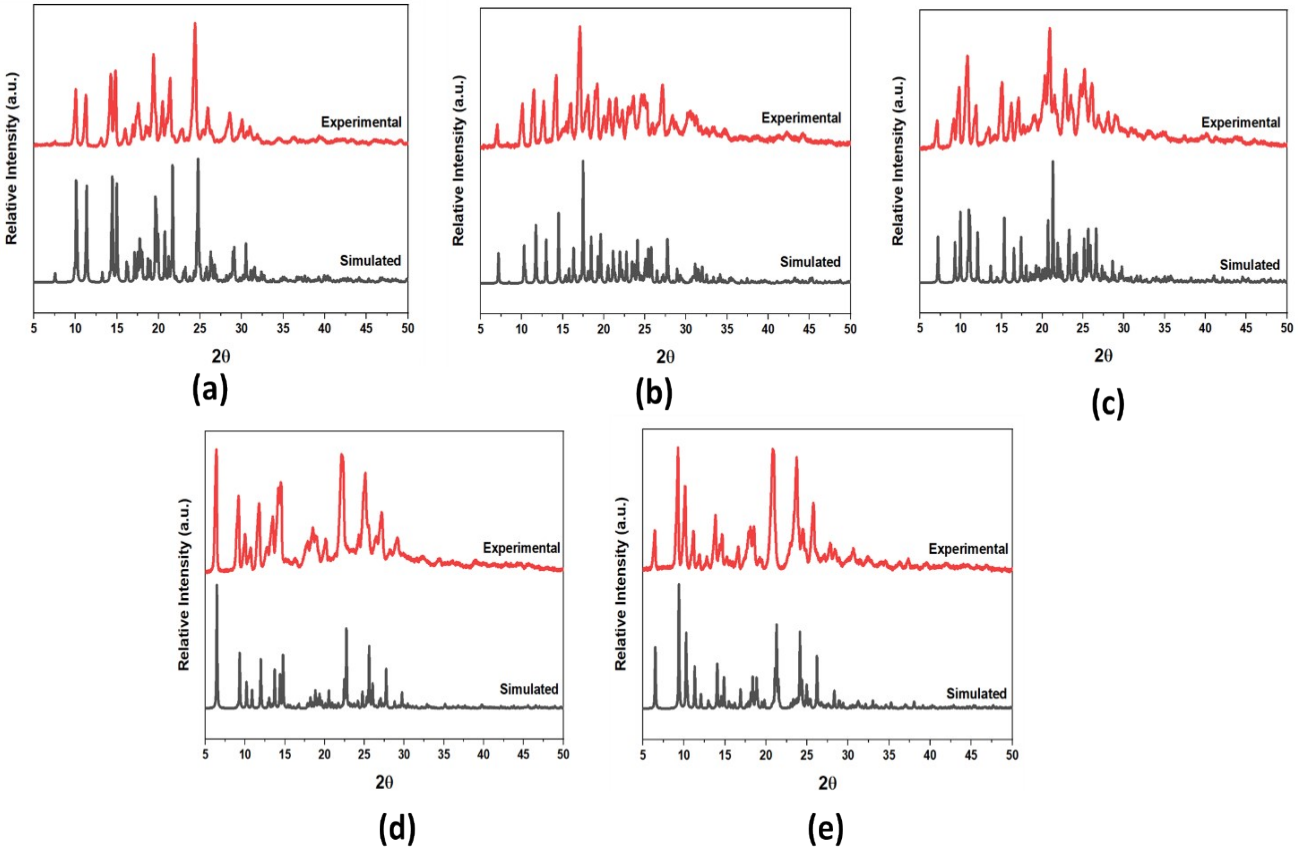


Figure S4. A comparative PXRD overlay of all the solid forms of ENSE (a) ENSE.MAL (a), (b) ENSE.MAL (b), (c) ENSE.PTH, (d) ENSE.SAL and (e) ENSE.SAC with its simulated pattern.

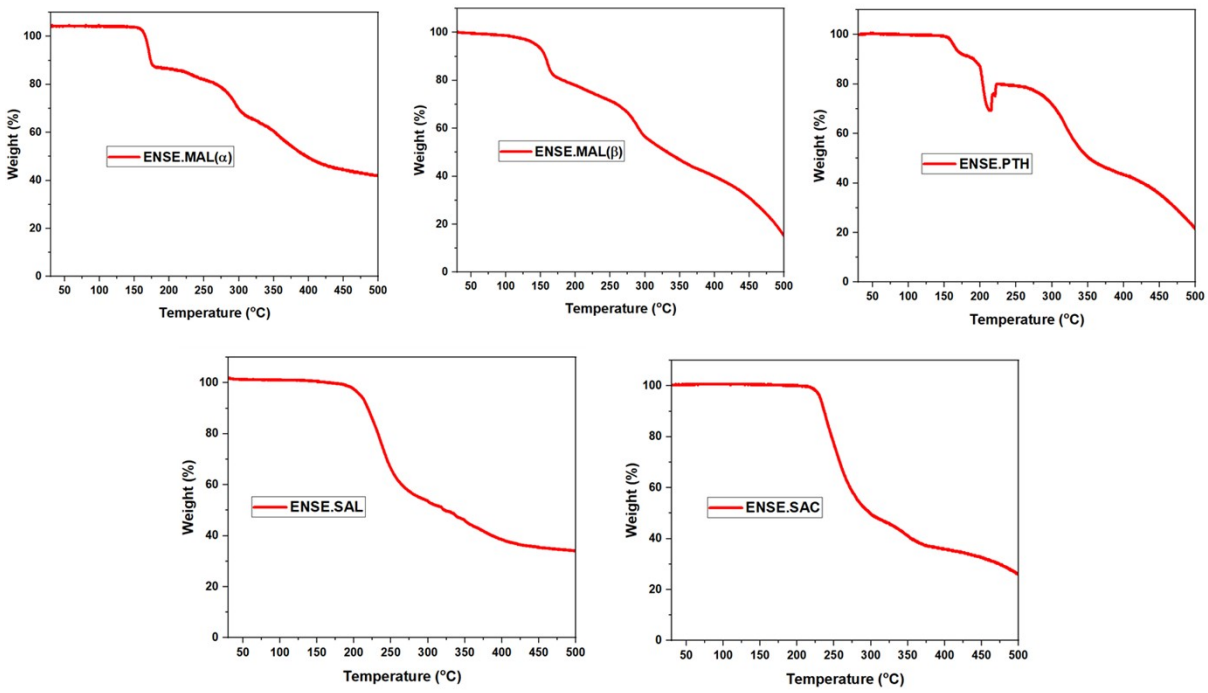
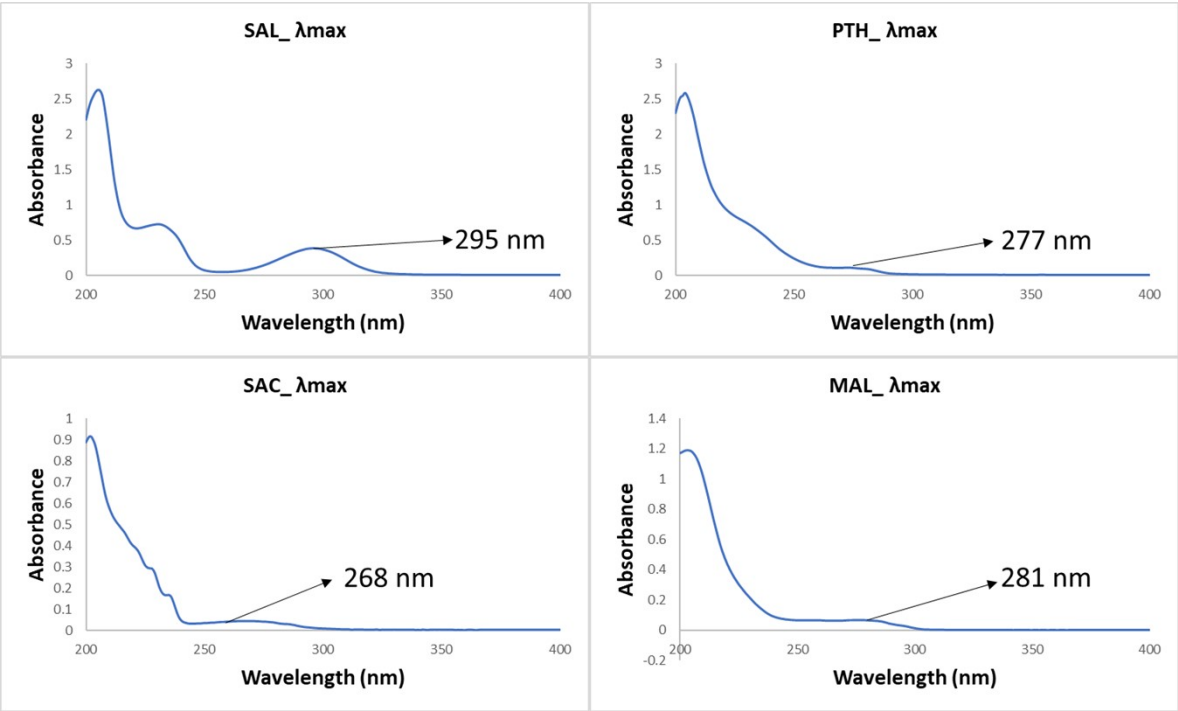
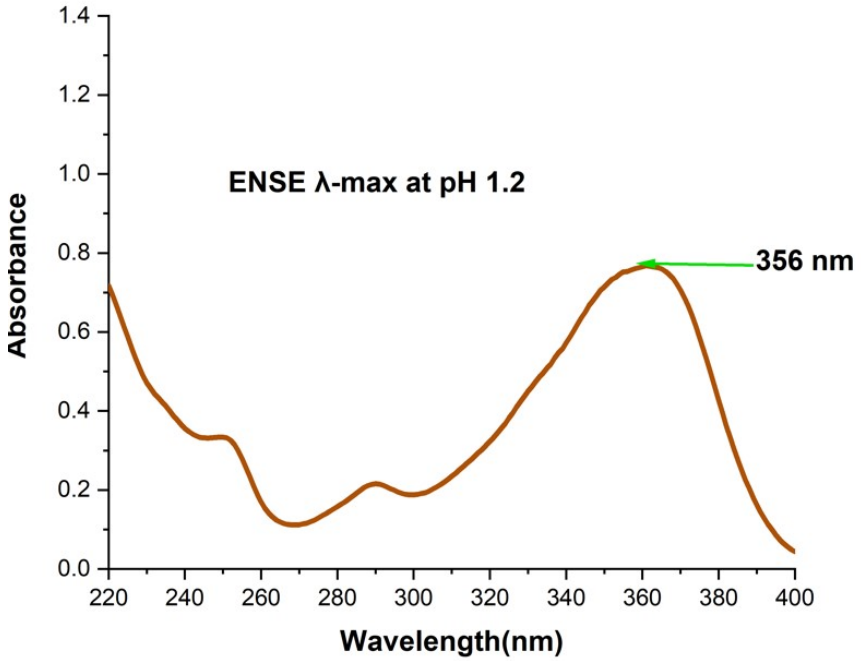
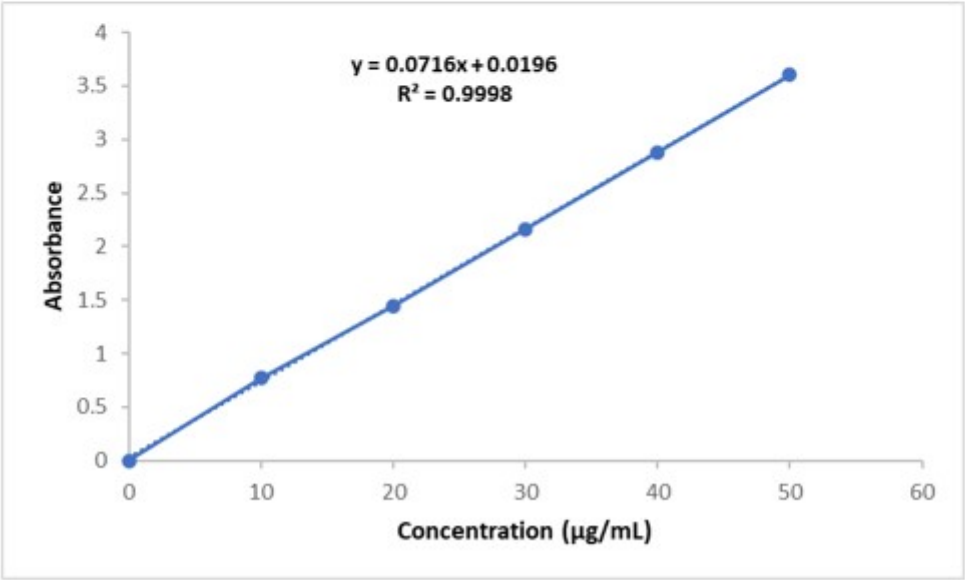


Figure S5. TGA profiles of various molecular adducts of ENSE.

<u>Details of the solubility parameters of solid forms of ENSE</u>

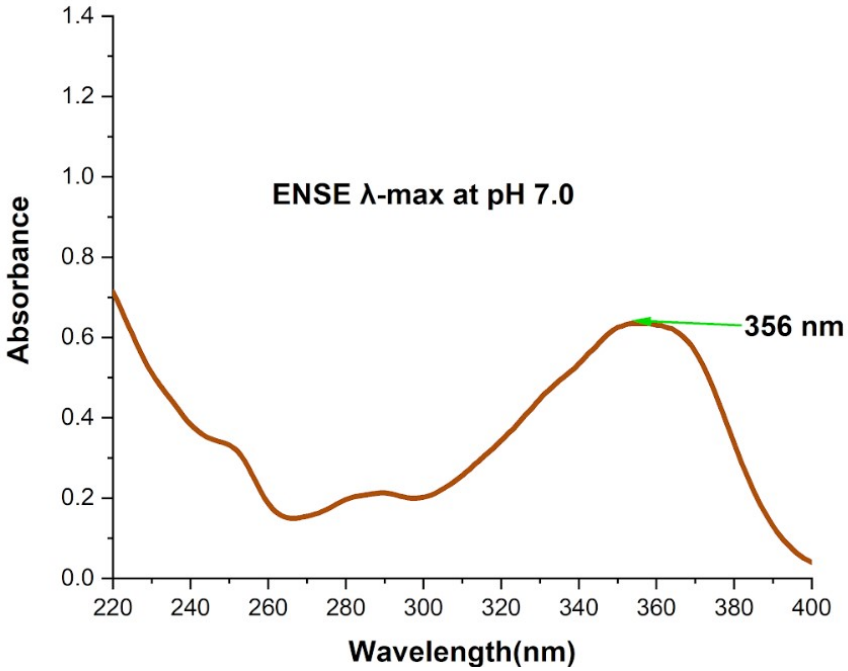

SAL_ λmax
Absorbance
Wavelength (nm)
295 nm
PTH_ λmax
277 nm
SAC_ λmax
268 nm
MAL_ λmax
281 nm


ENSE λ-max at pH 1.2
356 nm
Absorbance
Wavelength(nm)



Calibration graph of ENSE at pH 1.2.

S.No.	Sample Name	Absorbance			Estimated Standard Deviation	Average Absorbance	Average Concentration (mg/mL)	Final solid phase
1	ENSE	1.436	1.432	1.435	0.002	1.434	19.795	SALT
2	ENSE.MAL(α)	1.288	1.28	1.284	0.004	1.284	17.722	SALT
3	ENSE.MAL(β)	1.282	1.28	1.281	0.001	1.281	17.671	SALT
4	ENSE.PTH	0.124	0.127	0.125	0.002	0.126	1.7374	ENSE.PTH
5	ENSE.SAL	0.175	0.17	0.171	0.003	0.172	2.375	ENSE.SAL
6	ENSE.SAC	0.081	0.08	0.078	0.002	0.079	1.0861	ENSE.SAC



S.No.	Sample Name	Absorbance			Estimated Standard Deviation	Average Absorbance	Average Concentration (mg/mL)	Final solid phase
1	ENSE	1.886	1.883	1.885	0.002	1.884	0.029	ENSE
2	ENSE.MAL(α)	0.402	0.404	0.399	0.003	0.402	6.329	ENSE.MAL(α)
3	ENSE.MAL(β)	0.381	0.382	0.386	0.003	0.383	6.029	ENSE.MAL(β)
4	ENSE.PTH	0.36	0.362	0.36	0.001	0.361	5.689	ENSE.PTH
5	ENSE.SAL	0.115	0.117	0.116	0.001	0.116	1.8281	ENSE.SAL
6	ENSE.SAC	0.492	0.49	0.491	0.001	0.491	7.7376	ENSE.SAC

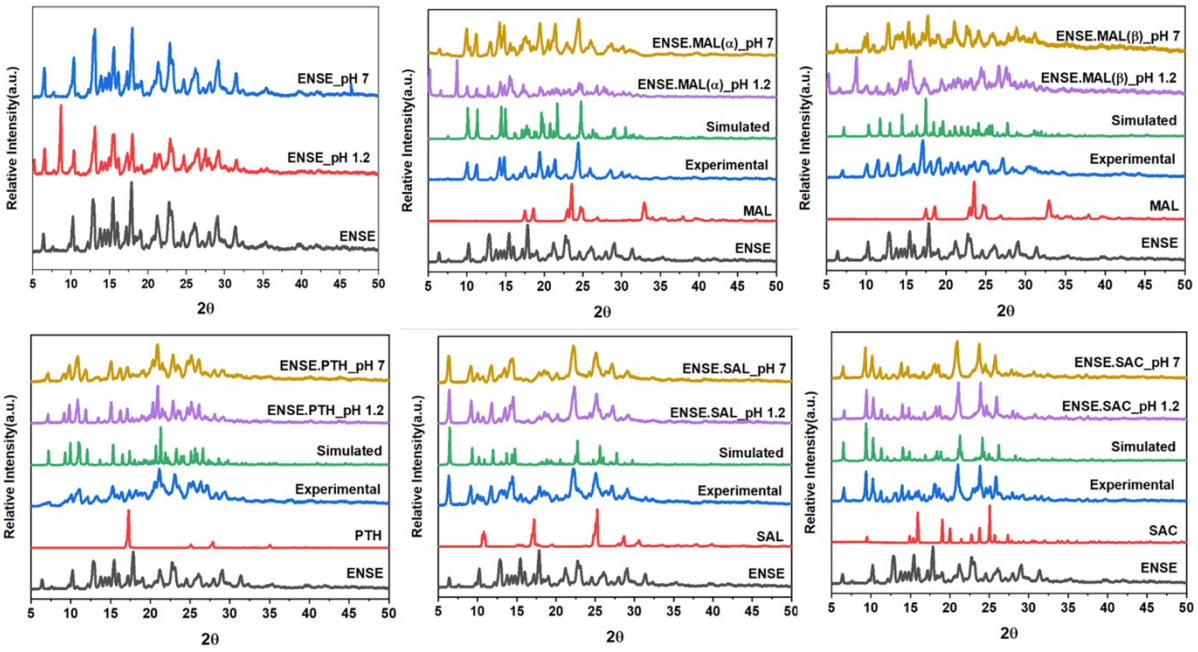


Figure S6. Overlay PXRD of ENSE solid forms before and after the solubility test, relative to their starting materials.

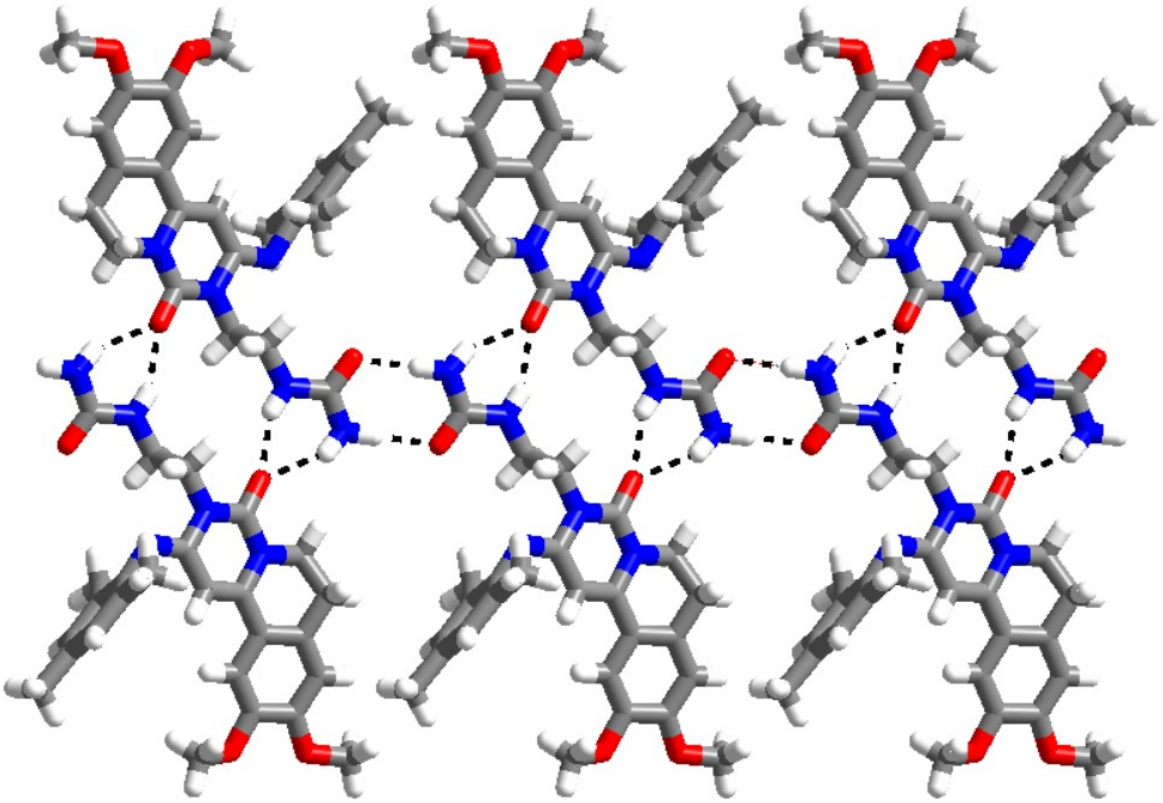


Figure S7. Illustration of molecular recognition between ENSE molecules.

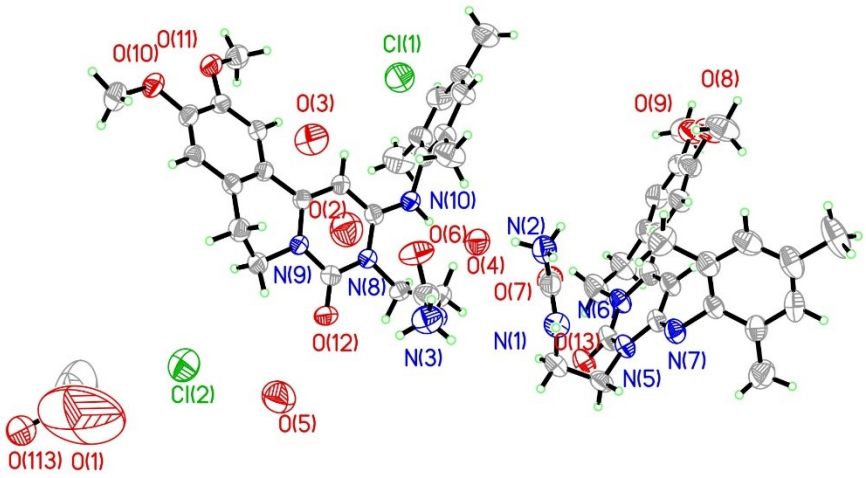


Figure S8. ORTEP view of ENSE.Cl. Herein, the ellipsoids are drawn with a 50% probability.

Table S3. Crystallographic Parameters of ENSE.Cl.

Parameters	**ENSE.Cl**
Formula	$2(C_{26}\ H_{32}\ N_5\ O_4)$. 1(C O). 2(Cl). 4(O)
M_r	1120.04
crystal shape	Needle
crystal colour	Colorless
crystal system	Triclinic
space group	$P\bar{1}$
T, K	273(2)
λ(Mo-K_α)/Å	0.71073

a/Å	12.371(8)
b/Å	13.385(7)
c/Å	17.690(2)
α/^{0}	93.64(1)
β/^{0}	105.06(2)
γ/^{0}	91.16(1)
V/Å^3	2821(2)
Z	2
D_c / g cm^{-3}	1.319
μ, mm^{-1}	0.186
2θ range [^{0}]	2.24-27.60
limiting indices	$-16 \leq h \leq 16$
	$-17 \leq k \leq 17$
	$-23 \leq l \leq 23$
F(000)	1180
total reflections	54109
unique reflections	13090
reflection at $I > 2\sigma(I)$	5756
No. of parameters	728
R_1, $I > 2\sigma(I)$	0.0751
wR_2 $I > 2\sigma(I)$	0.2536
GoF on F^2	1.110
CCDC No.	2349985

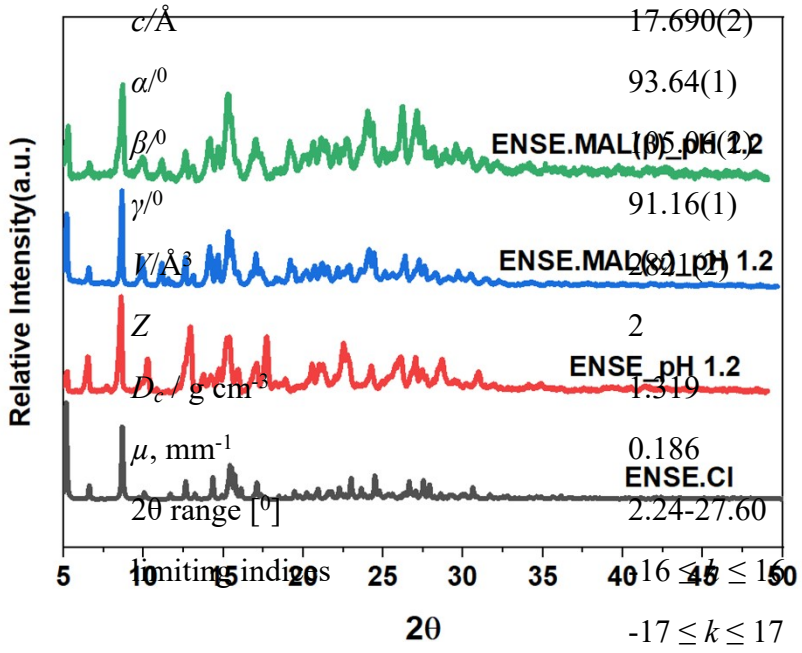


Figure S9.

Following the solubility test, a comparative PXRD overlay of all the solid forms of ENSE showed the development of discrete, stable adducts that matched the simulated pattern of ENSE.Cl.