Flutamide degradation driven by sulfonic acids: An unforeseen salts and salt polymorphs of degraded flutamide impurity

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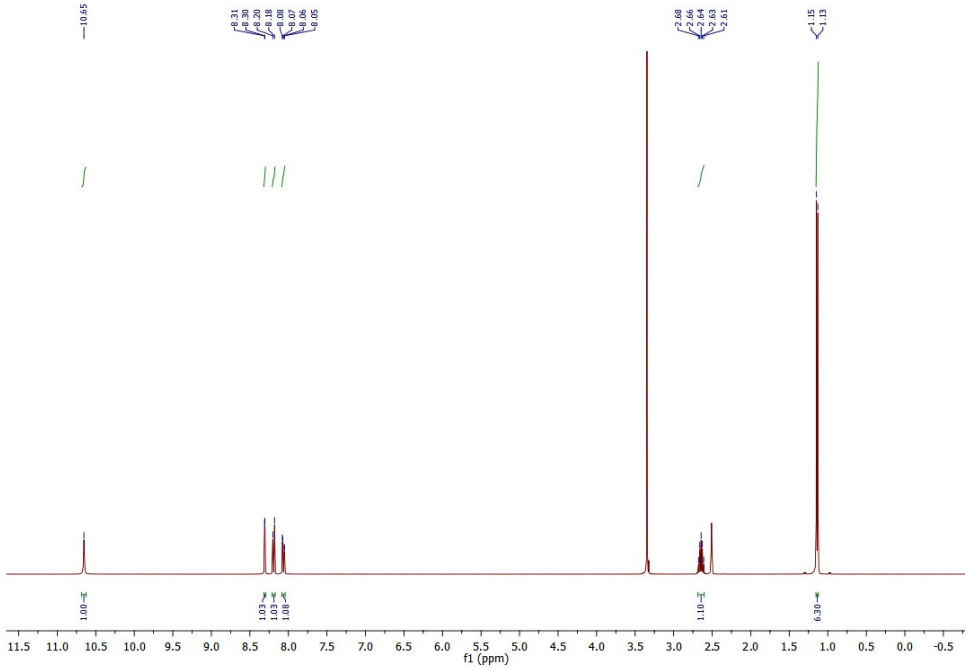

Figure S1.[1]H NMR spectra of Flutamide.

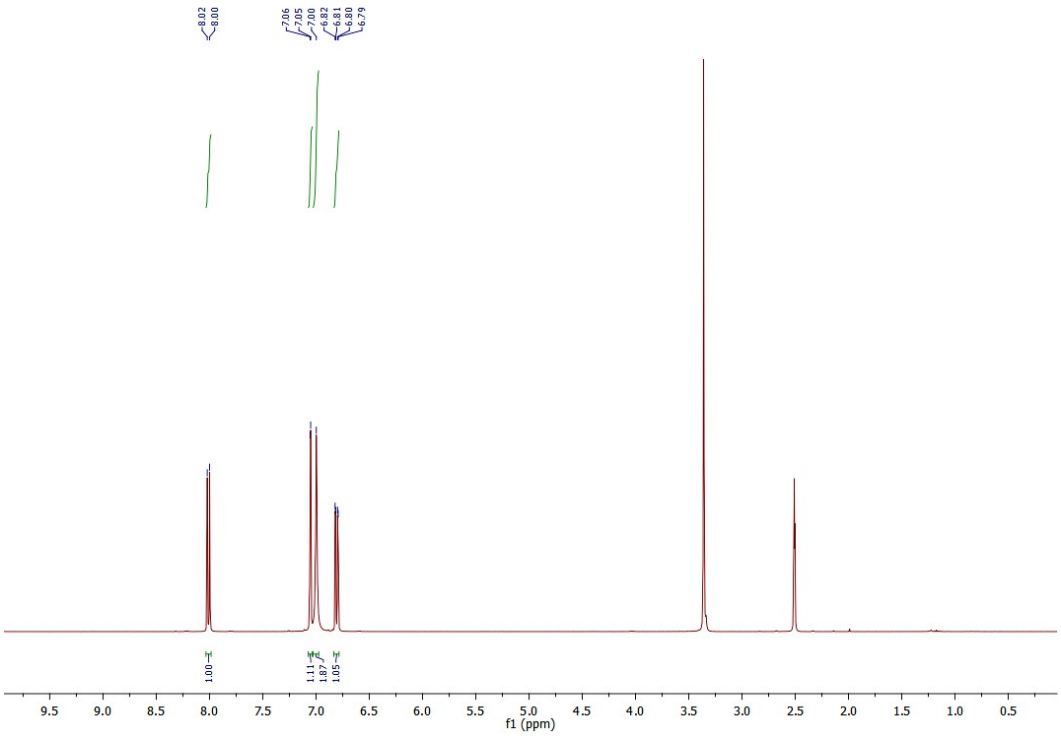

Figure S2.[1]H NMR spectra of Flu.D.

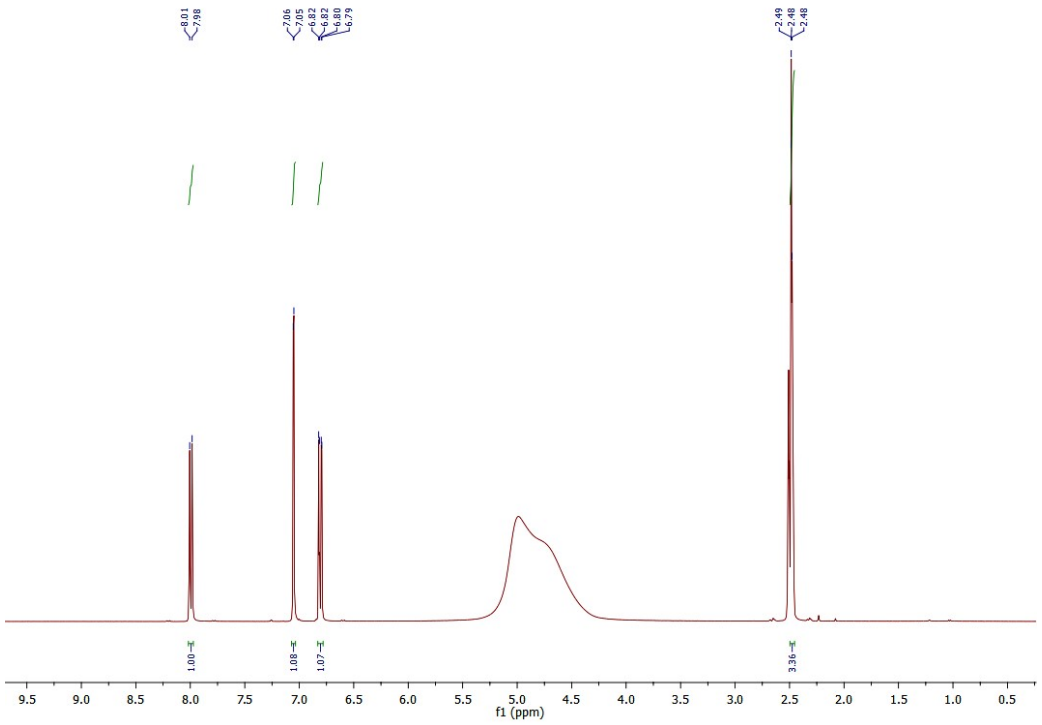

Figure S3.[1]H NMR spectra of Flu.D-MSA (1:1).

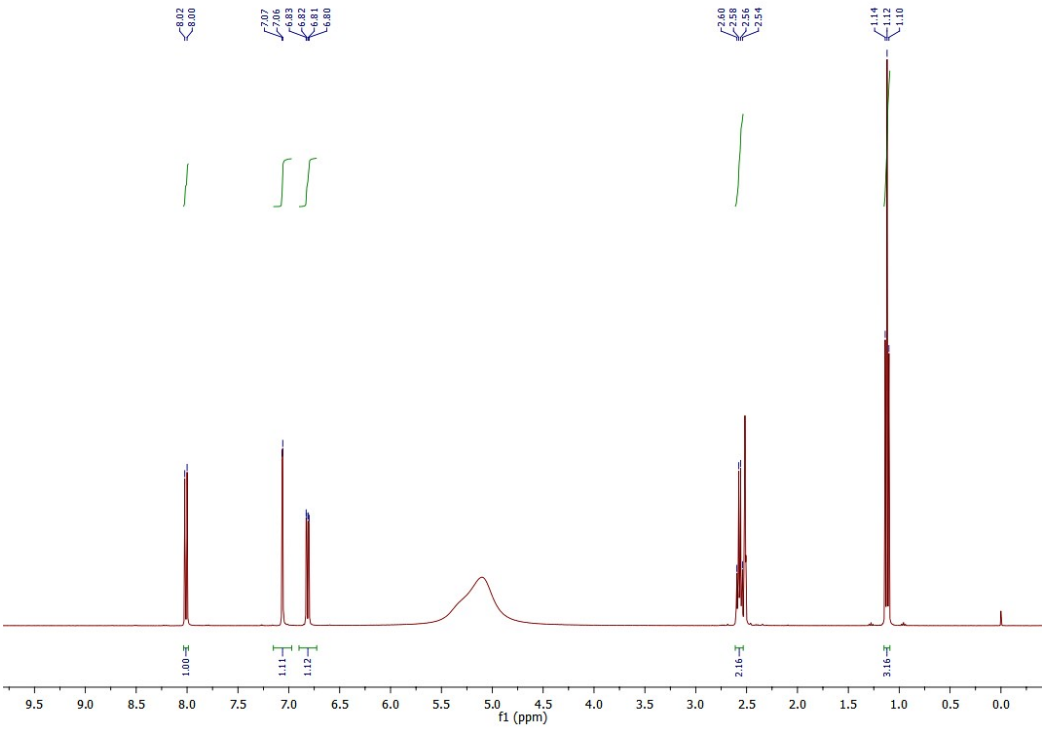

Figure S4.[1]H NMR spectra of Flu.D-ESA (2:2).

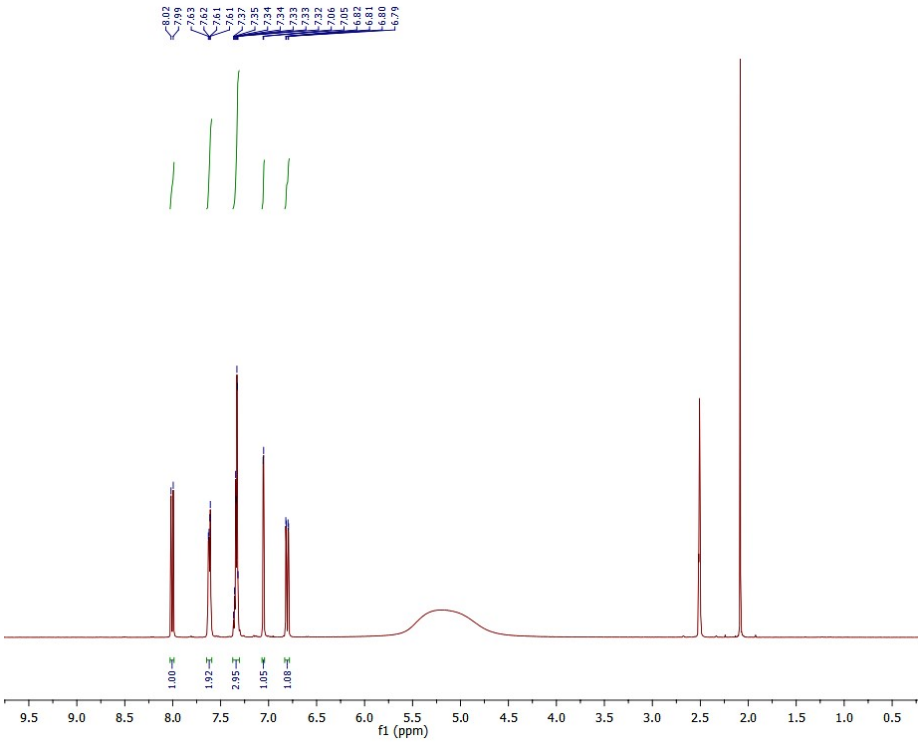

Figure S5.[1]H NMR spectra of Flu.D-BSA (2:2).

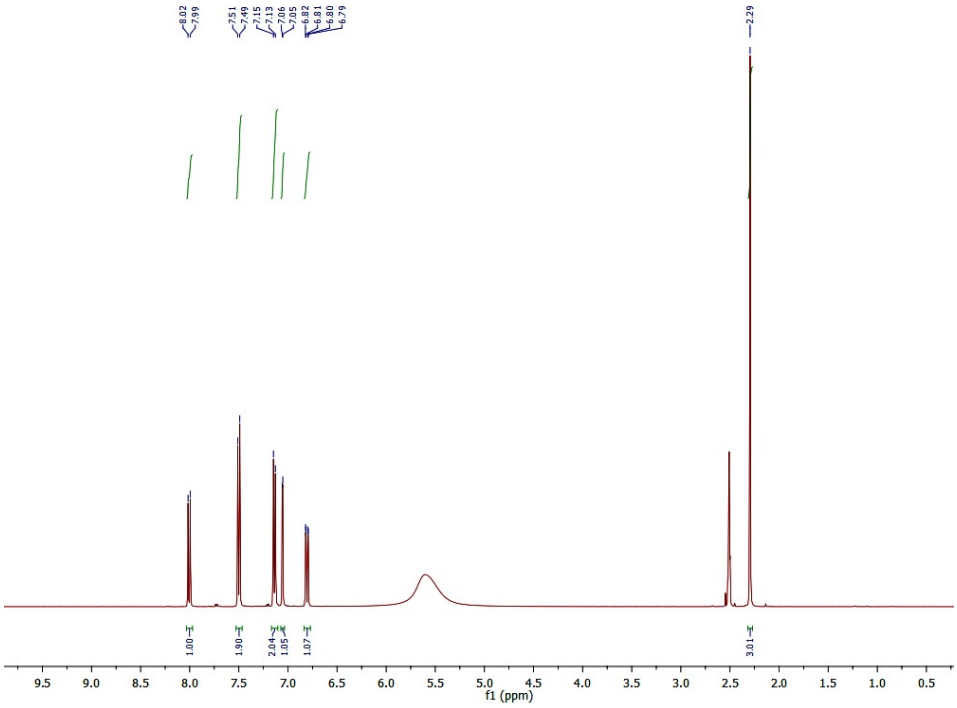

Figure S6.[1]H NMR spectra of Flu.D-PTSA (2:2).

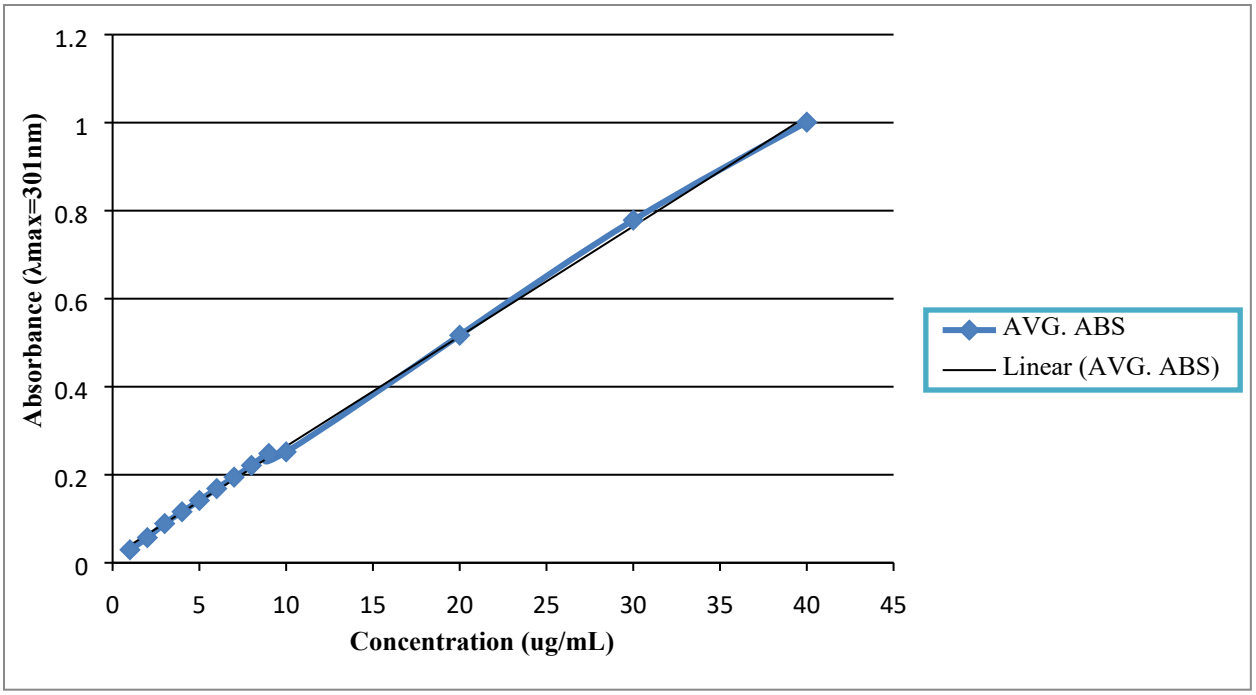

Figure S7. Linearity curve of flutamide (in water) using UV-Visible spectroscopy for dissolution studies.

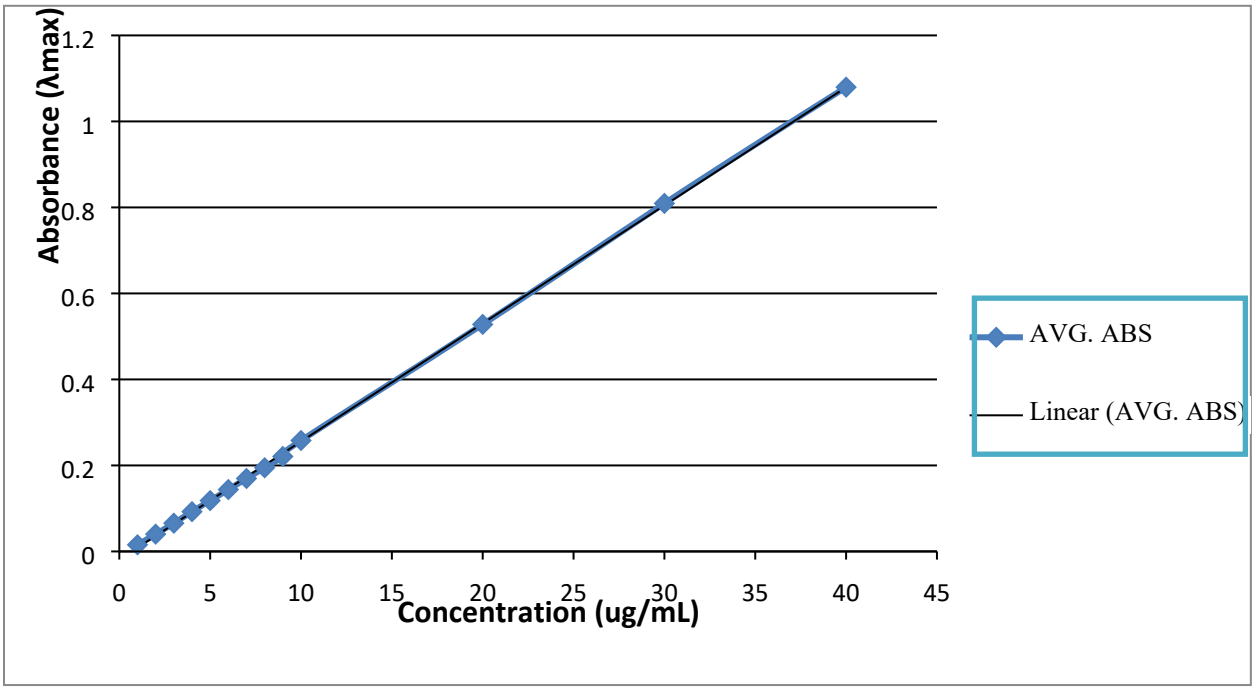

Figure S8. Linearity curve of flutamide (in pH 1.2) using UV-Visible spectroscopy for dissolution studies.

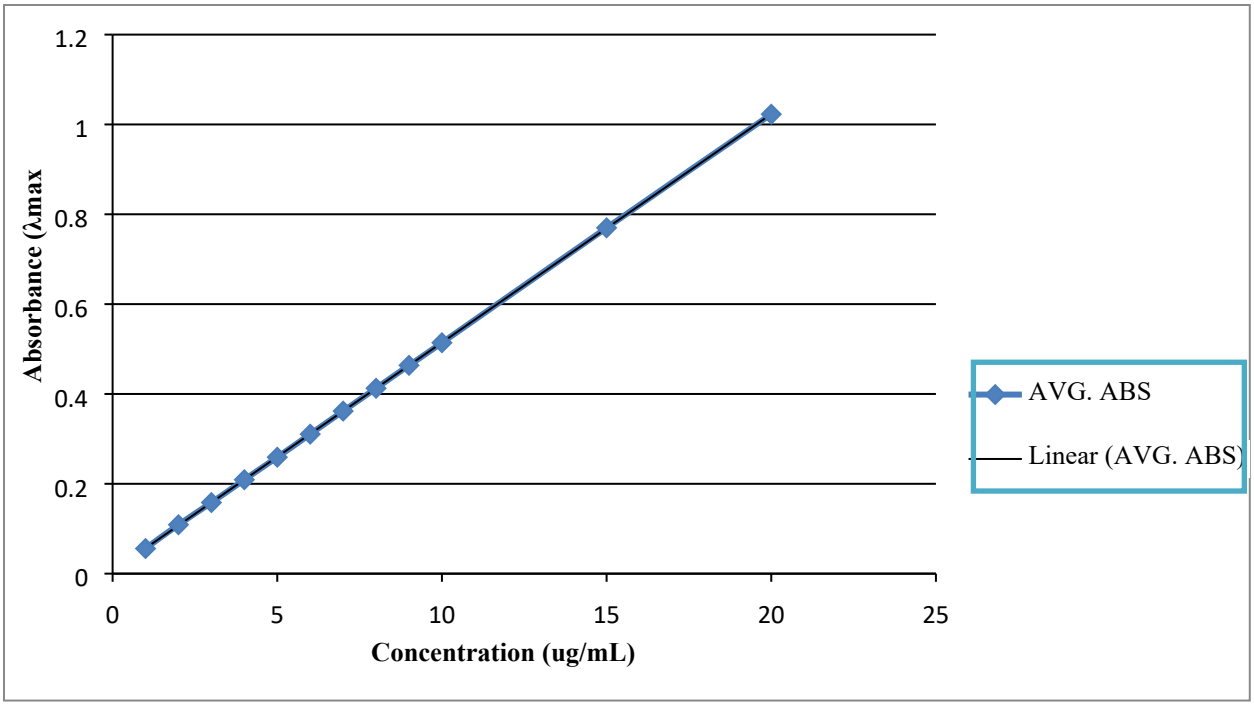

Figure S9. Linearity curve of Flu.D (in water) using UV-Visible spectroscopy for dissolution studies.

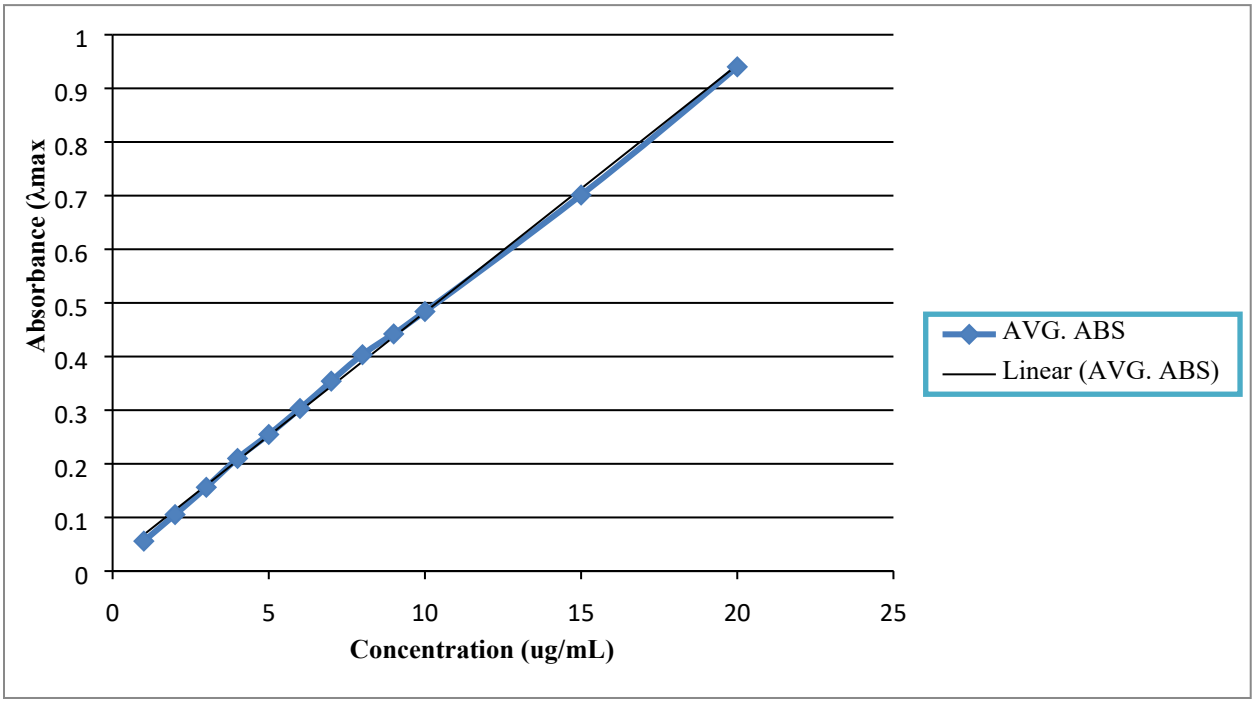

Figure S10.Linearity curve of Flu.D (in pH 1.2) using UV-Visible spectroscopy for dissolution studies.

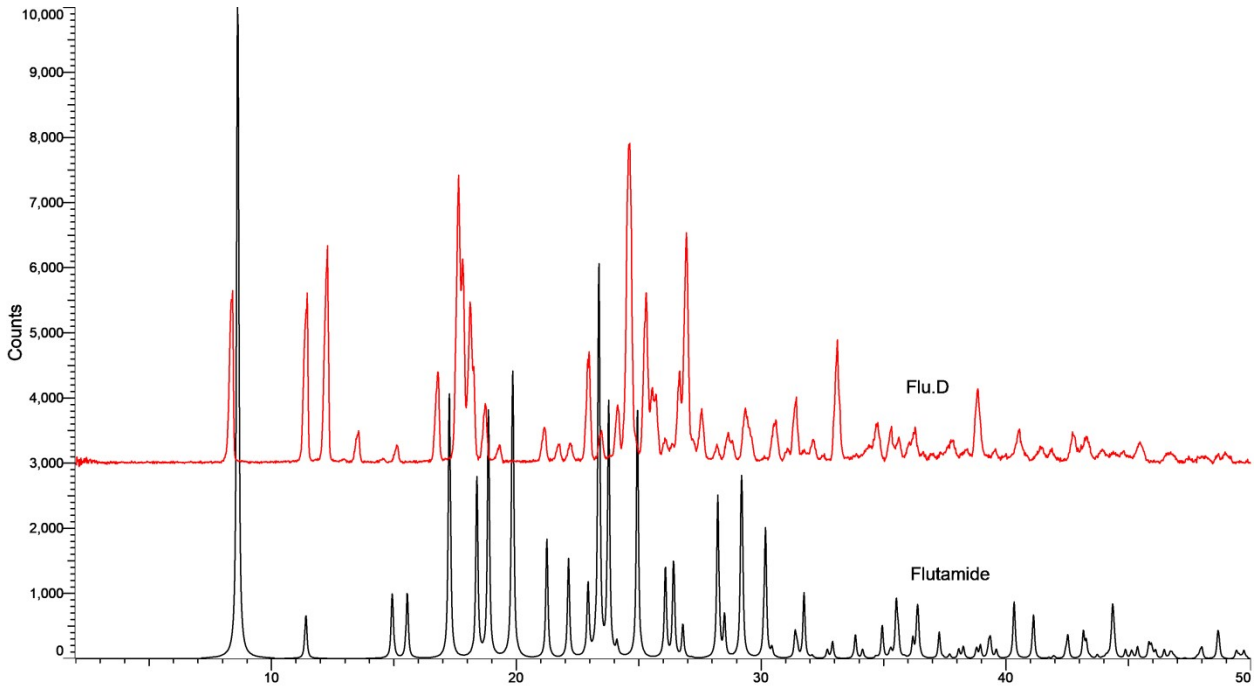

Figure S11. PXRD overlay of flutamide with the impurity (Flu.D) showing distinct peaks.

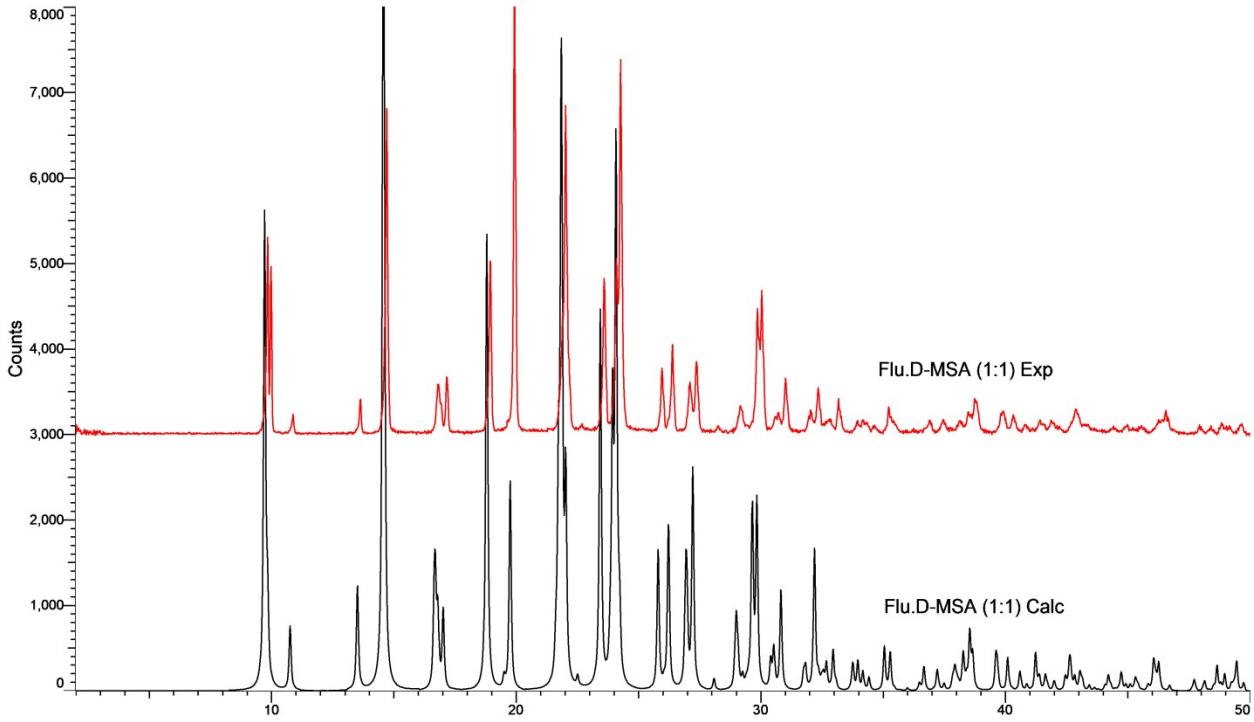

Figure S12. Comparison of simulated (Flu.D-MSA (1:1) Calc) and experimental (Flu.D-MSA (1:1)Exp) PXRD patterns, demonstrating phase purity of the salts.

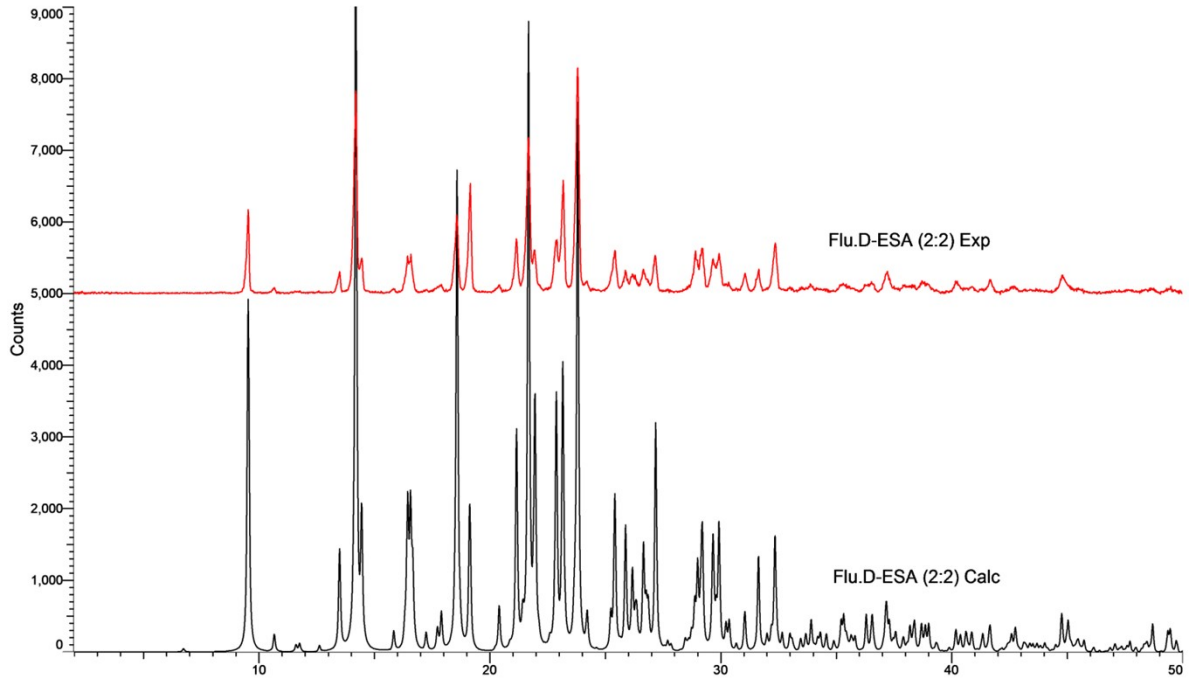

Figure S13. PXRD overlay of Flu.D-ESA (2:2) simulated pattern (Flu.D-ESA (2:2) Calc) with phase pure experimental pattern (Flu.D-ESA (2:2) Exp).

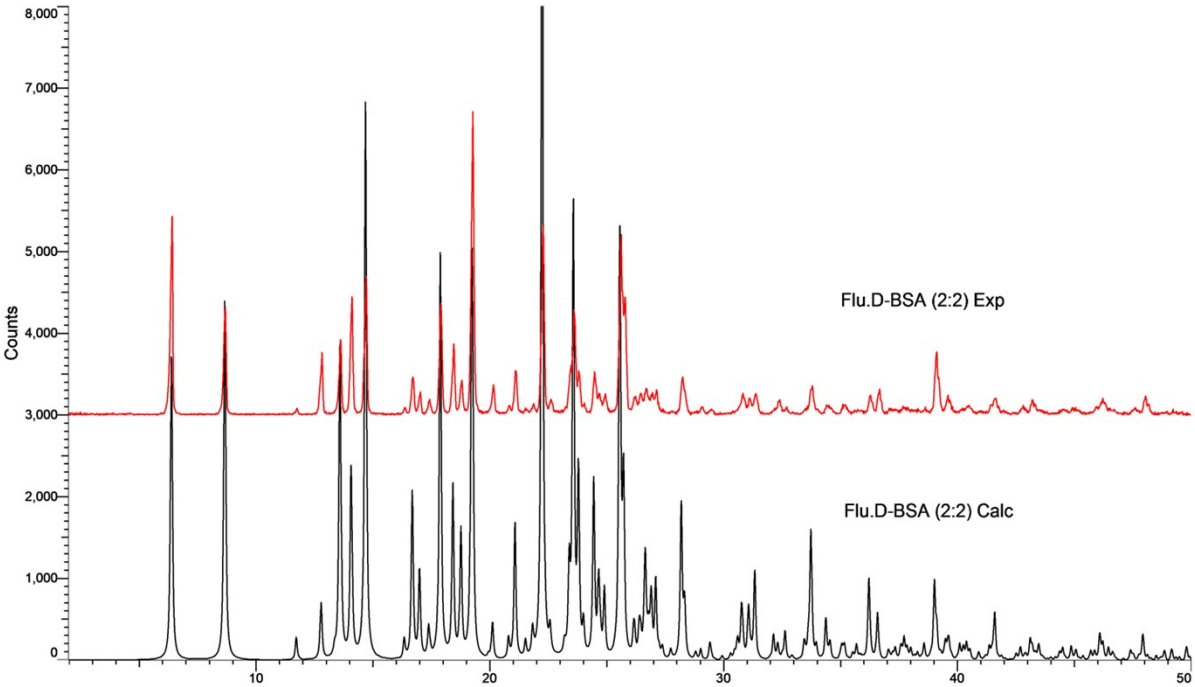

Figure S14. PXRD overlay of Flu.D-BSA (2:2) simulated pattern (Flu.D-BSA (2:2) Calc) with phase pure experimental pattern (Flu.D-BSA (2:2) Exp).

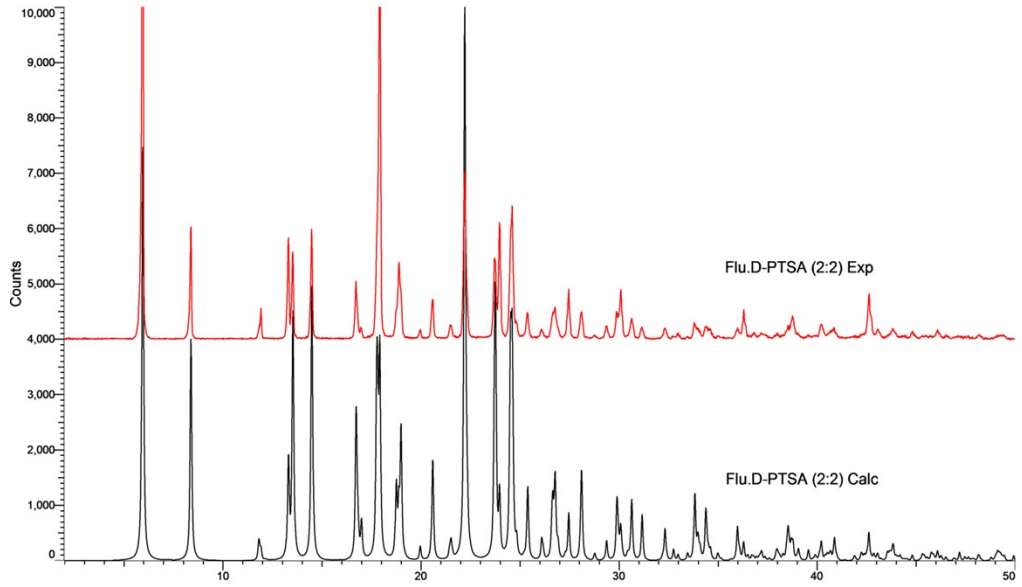

Figure S15. Overlay of calculated and experimental PXRD patterns of Flu.D-PTSA (2:2) composition, indicating the phase purity.

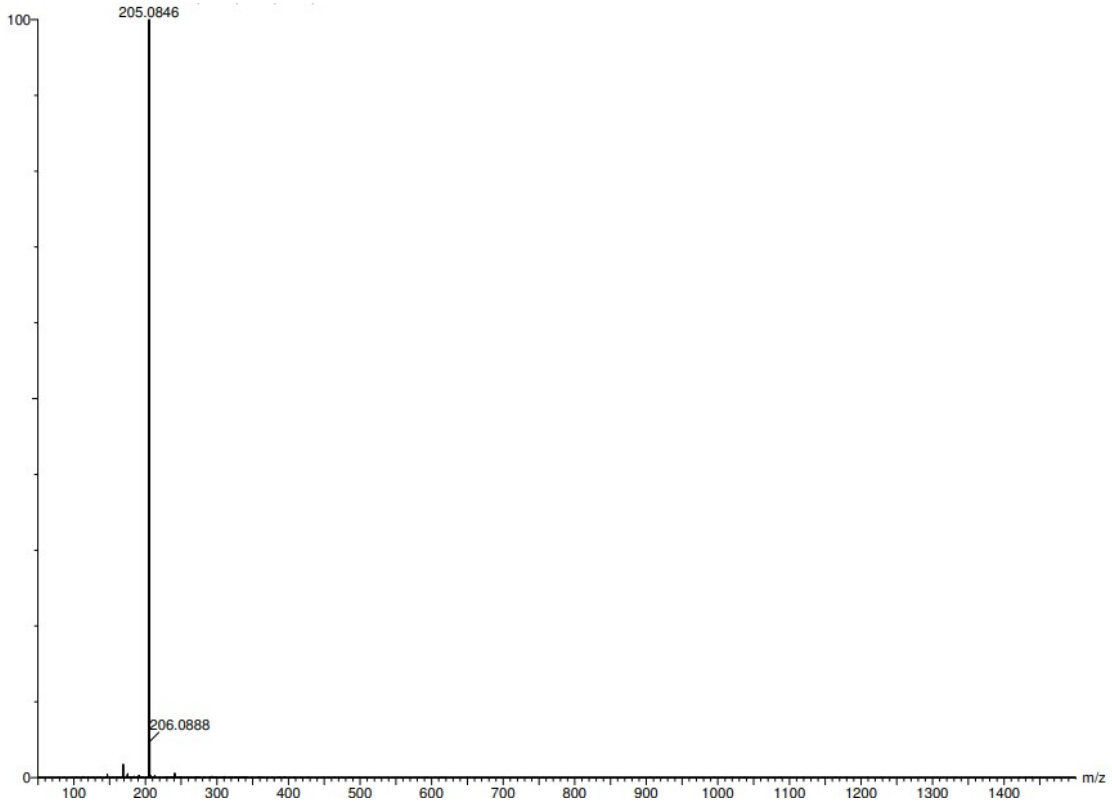

Figure S16. ESI-QTOF MS spectra of Flu.D.

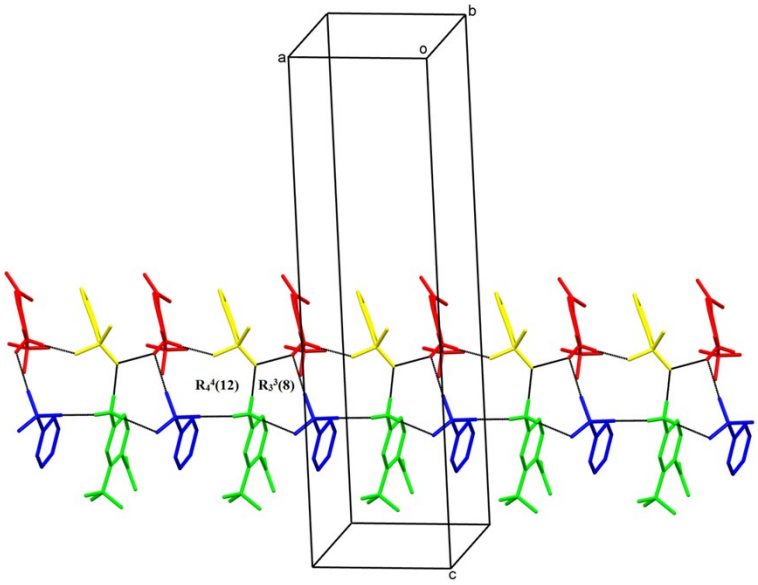

Figure S17. Part of crystal packing of Flu-BSA 6:6 showing one dimensional chain sets and tetramer motifs formed between A and B molecules which aggregate into 2D sheets. H atoms that are not involved in hydrogen bonding have been omitted for clarity. Hydrogen bonds are shown as dashed lines. The green color represents Flu.D A molecule, BSA A (blue), Flu.D B (red), BSA B(yellow).

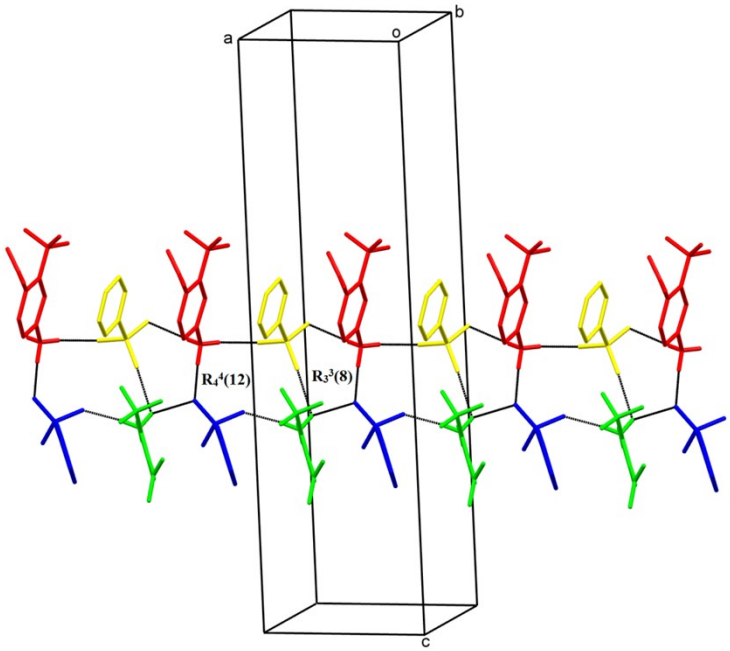

Figure S18. Part of crystal packing of Flu.D-BSA 6:6 showing infinite 1D chain and tetrameric sets between C and D molecules which in turn aids to form 2D sheets. H atoms that are not

involved in hydrogen bonding have been omitted for clarity. Hydrogen bonds are shown as dashed lines. The green color indicates Flu.D molecule C, BSA C (blue), Flu.D D (yellow), BSA D molecule (red).

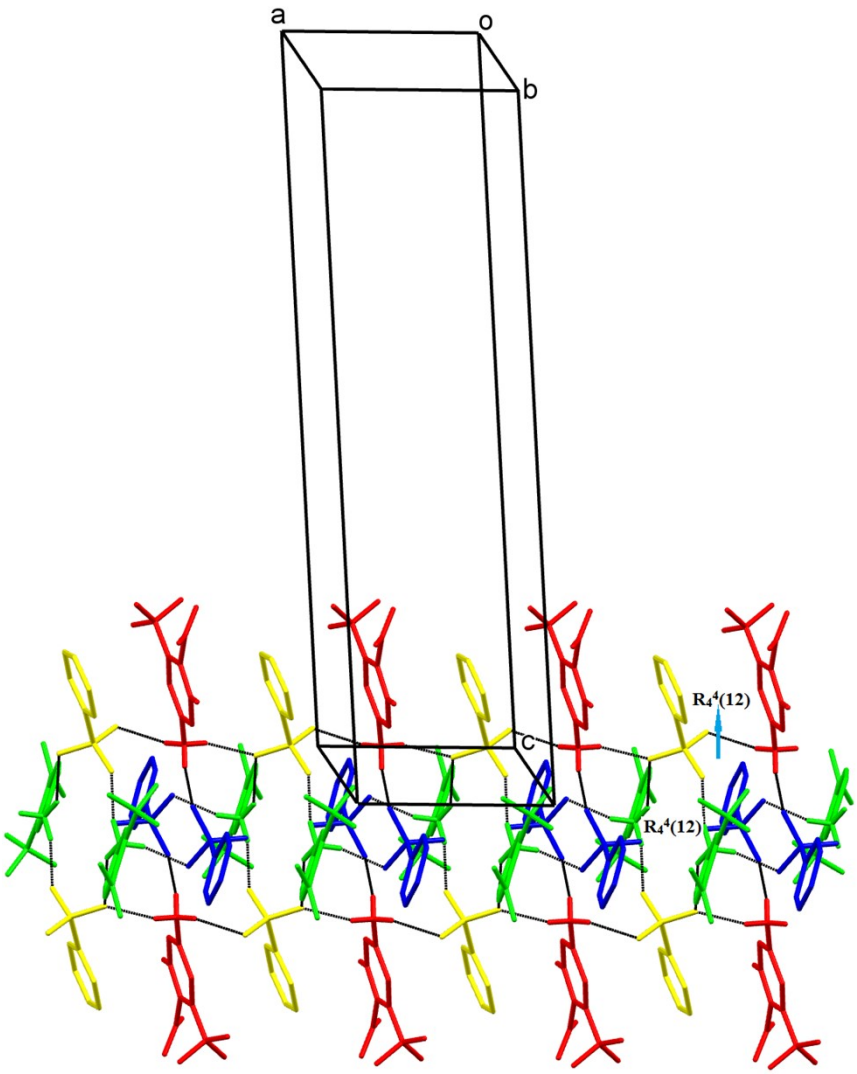

Figure S19. Part of crystal structure of Flu.D-BSA 6:6 which show 1D chain formed between F molecules of Flu.D and BSA along with tetrameric units generated between E and F molecules of Flu.D and BSA. H atoms that are not involved in hydrogen bonding have been omitted for clarity. Hydrogen bonds are shown as dashed lines. The green color represents Flu.D E molecule, BSA E (blue), Flu.D F (yellow), and BSA F (red).

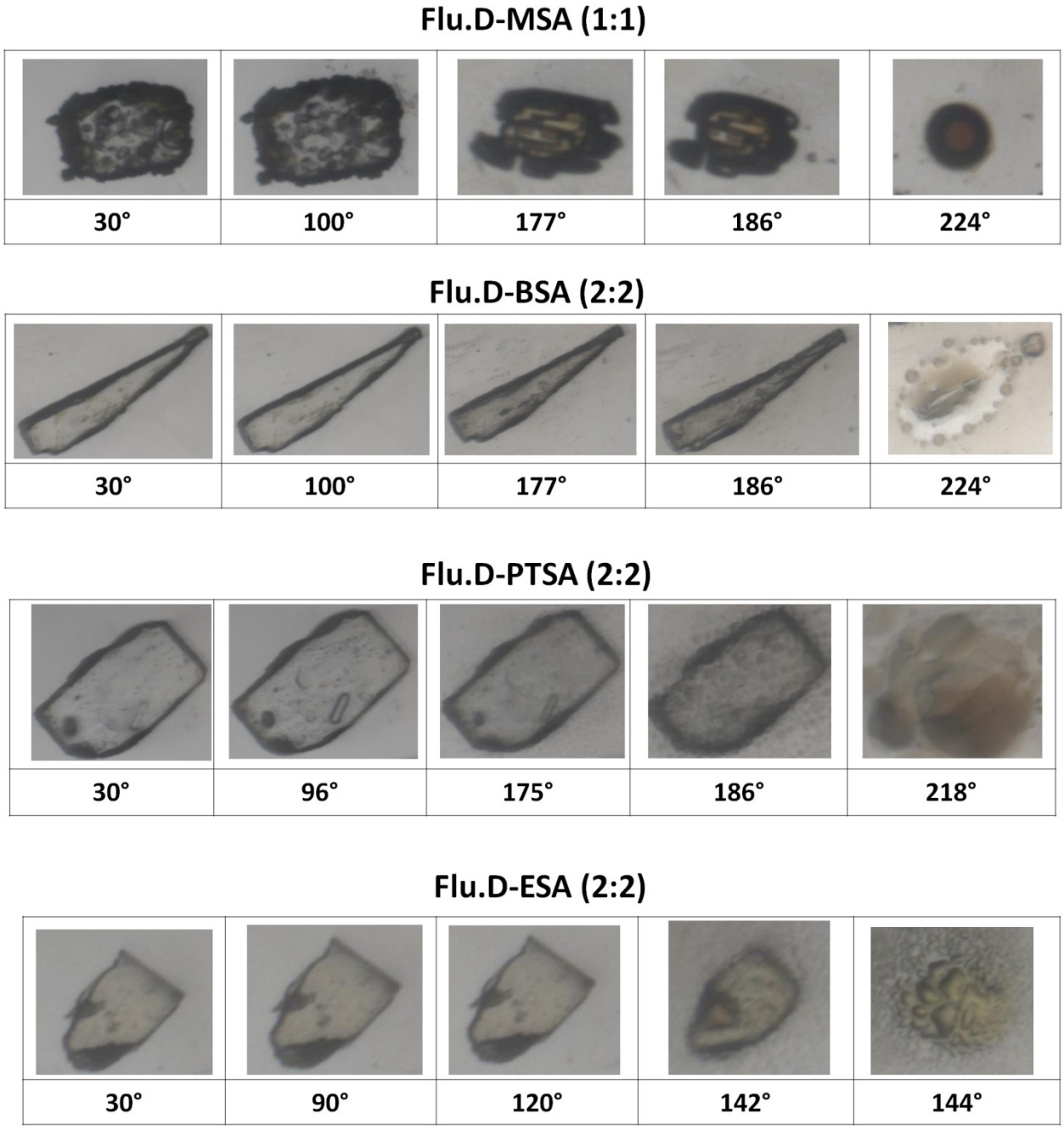

Figure S20. HSM studies demonstrate phase transformation in the salts, visually apparent as crystal darkening.

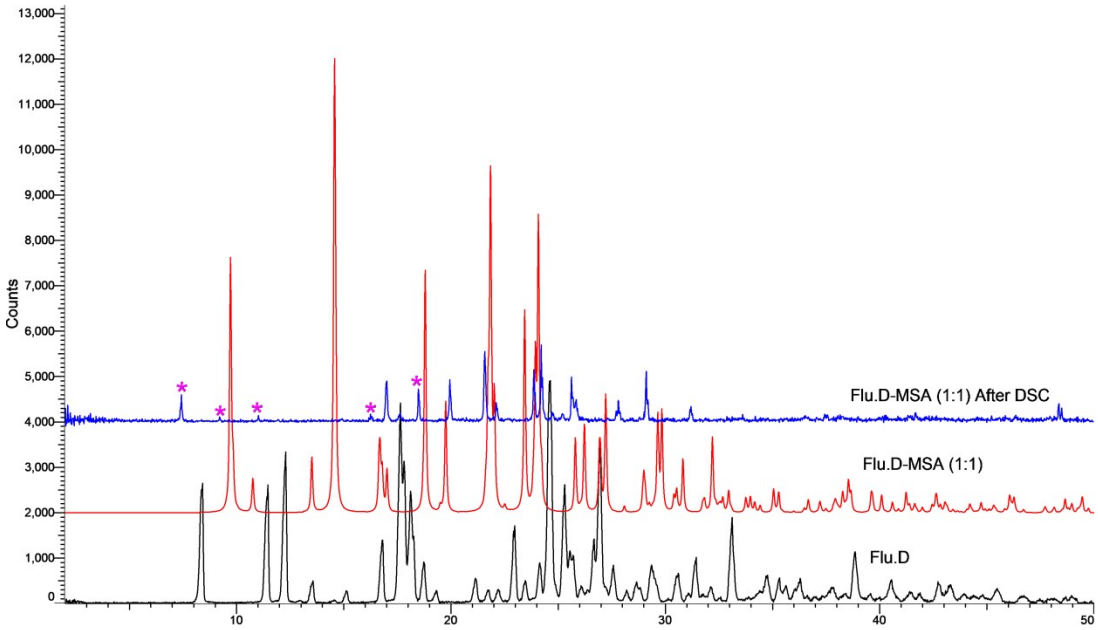

Figure S21. PXRD overlay comparing Flu.D, Flu.D-MSA (1:1) before and after DSC (Flu.D-MSA (1:1) After DSC) which showcases the phase transformation. * indicates the unknown phase.

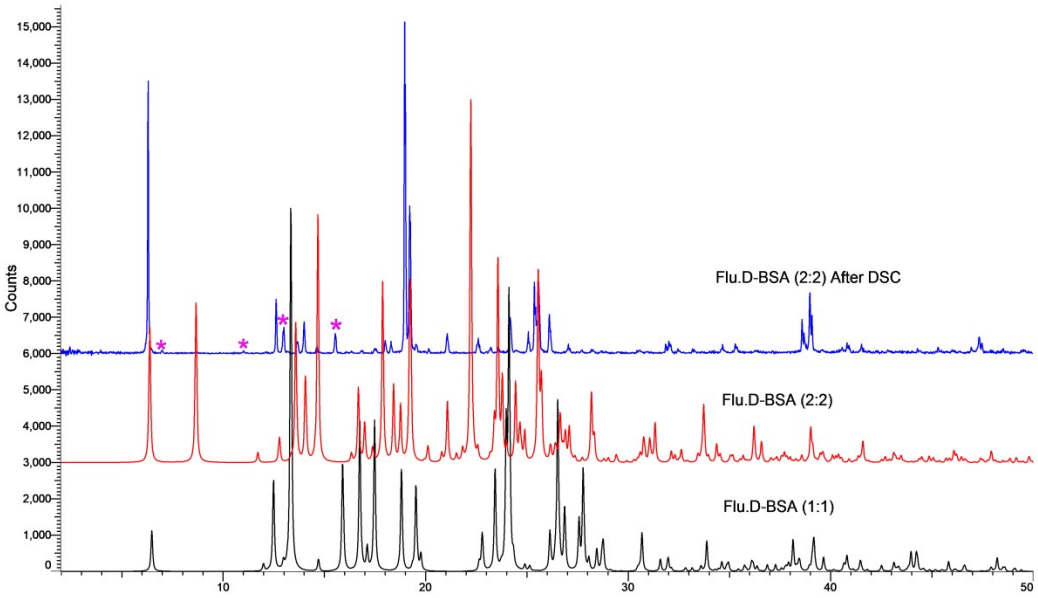

Figure S22. PXRD overlay of Flu.D-BSA (1:1) and Flu.D-BSA (2:2) which was used for DSC analysis with the obtained form after phase transformation (Flu.D-BSA (2:2) After DSC) experiment. * indicates the unknown phase.

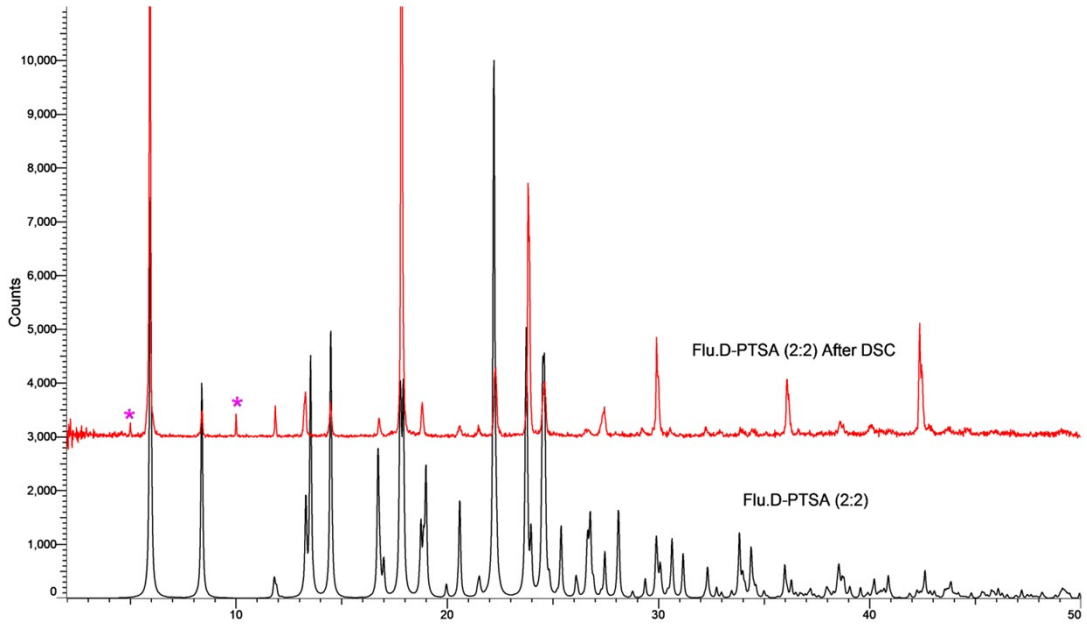

Figure S23. PXRD overlay of Flu.D-PTSA (2:2) which was used for DSC analysis with the obtained form after phase transformation (Flu.D-PTSA (2:2) After DSC) experiment. * indicates the unknown phase.

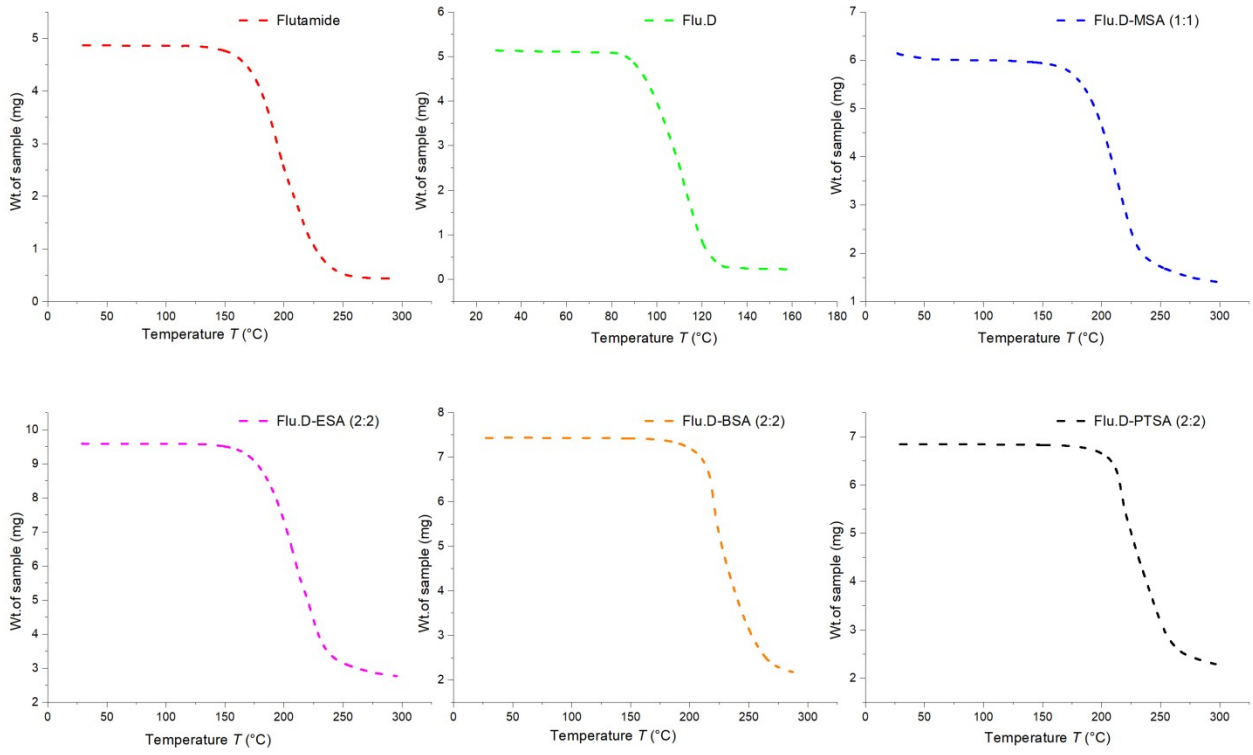

Figure S24. TGA data of newly obtained salts.

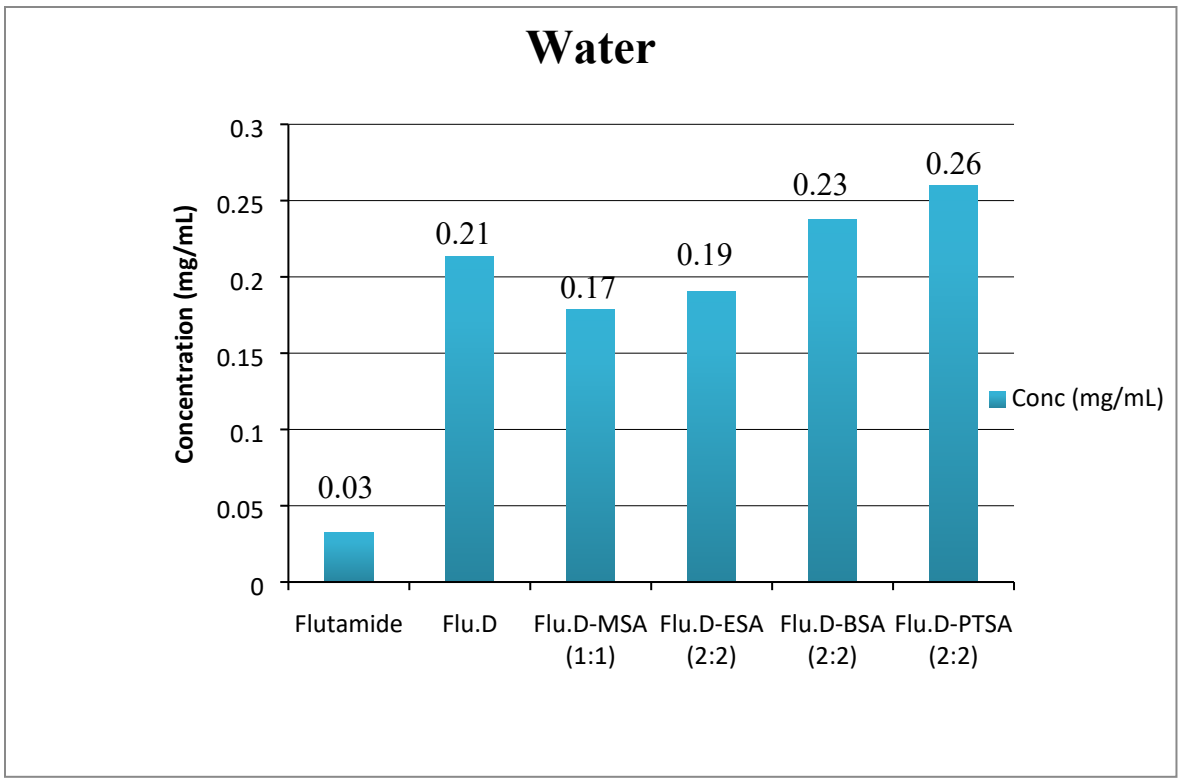

Figure S25. Solubility data of flutamide, Flu.D and its salts performed in water media.

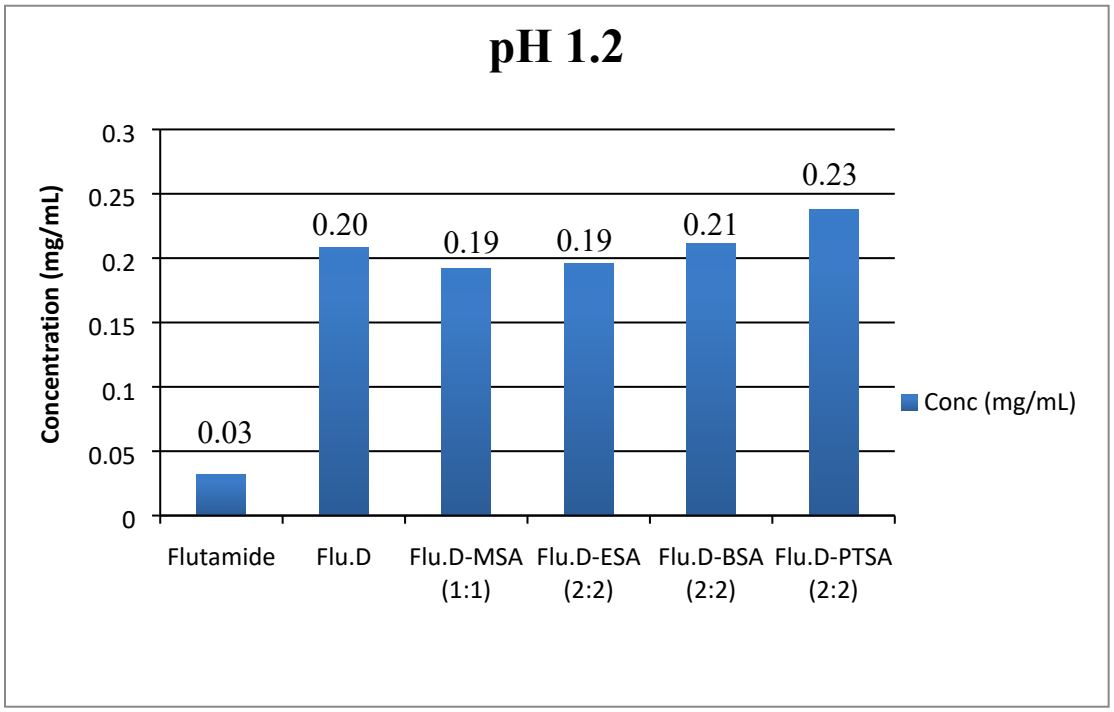

Figure S26. Solubility data of flutamide, Flu.D and its salts performed in pH 1.2 buffer media.

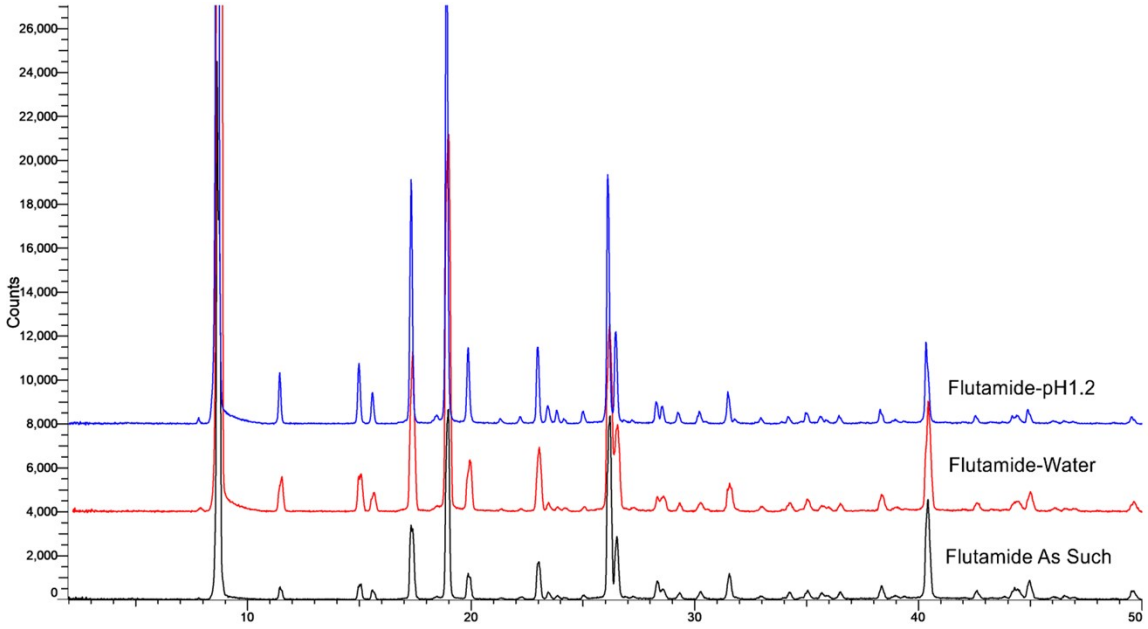

Figure S27. PXRD overlay of flutamide as such with residues recovered after solubility study (24hr) in water (Flutamide-Water) and pH 1.2 (Flutamide-pH 1.2) media.

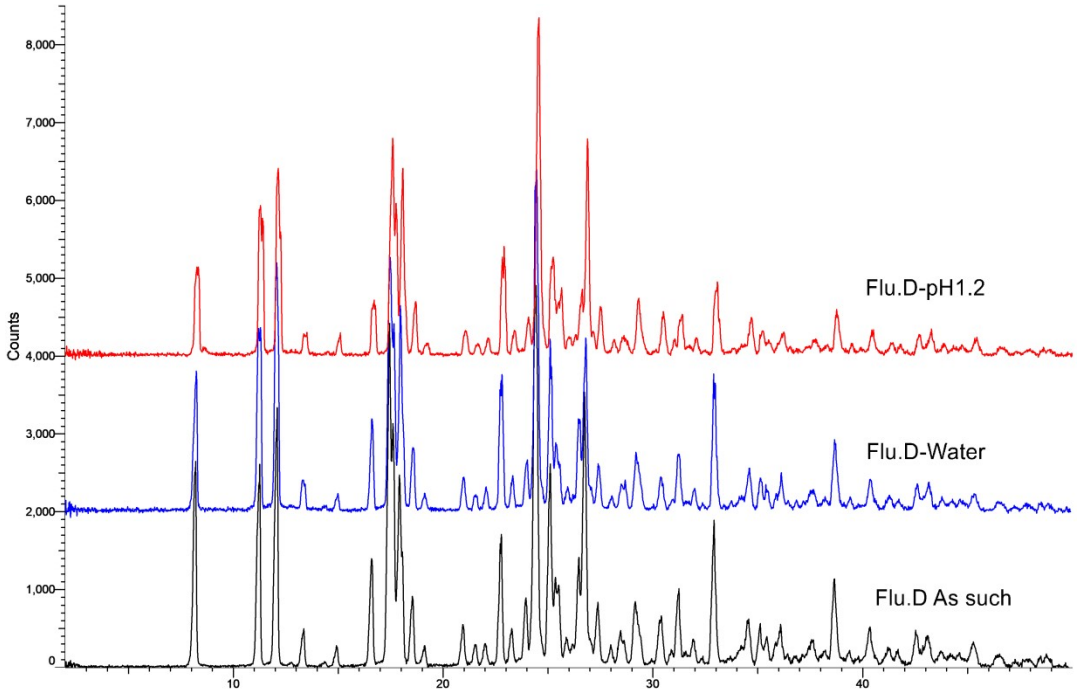

Figure S28. PXRD overlay of Flu.D parent (Flu.D as such) with residues recovered from water (Flu.D-Water) and pH 1.2 (Flu.D-pH 1.2) after 24hrs.

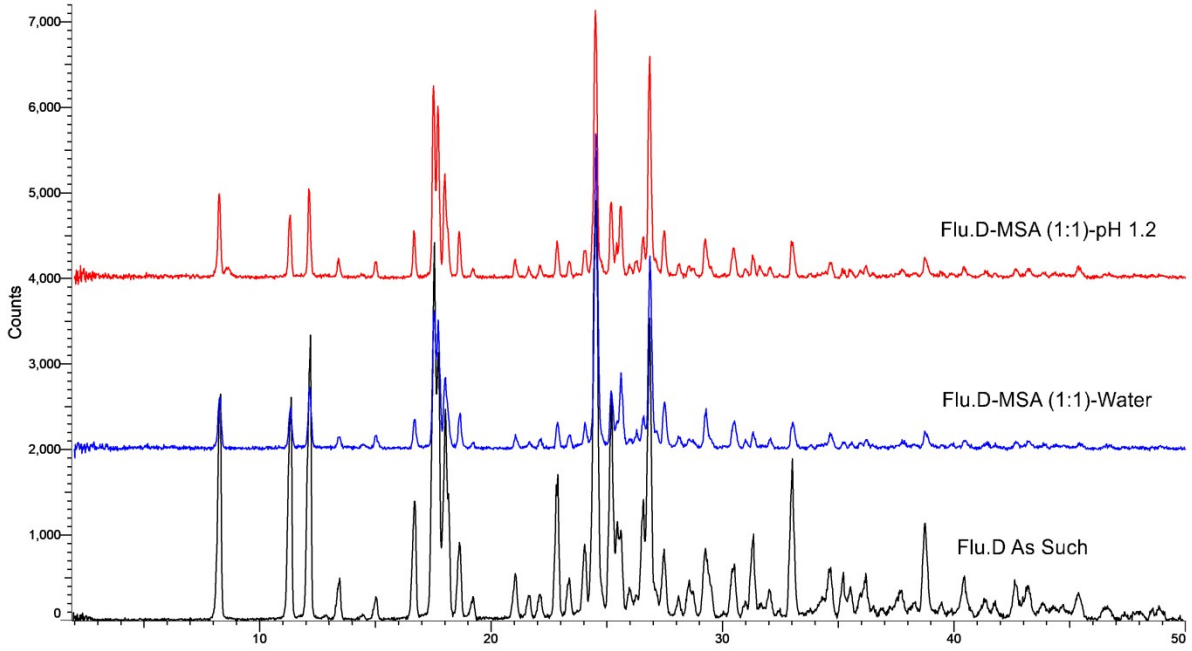

Figure S29. PXRD overlay of Flu.D parent (Flu.D as such) with residues recovered after equilibrium solubility study (24hr) in water (Flu.D-MSA (1:1)-Water) and pH 1.2 (Flu.D-MSA (1:1)-pH 1.2).

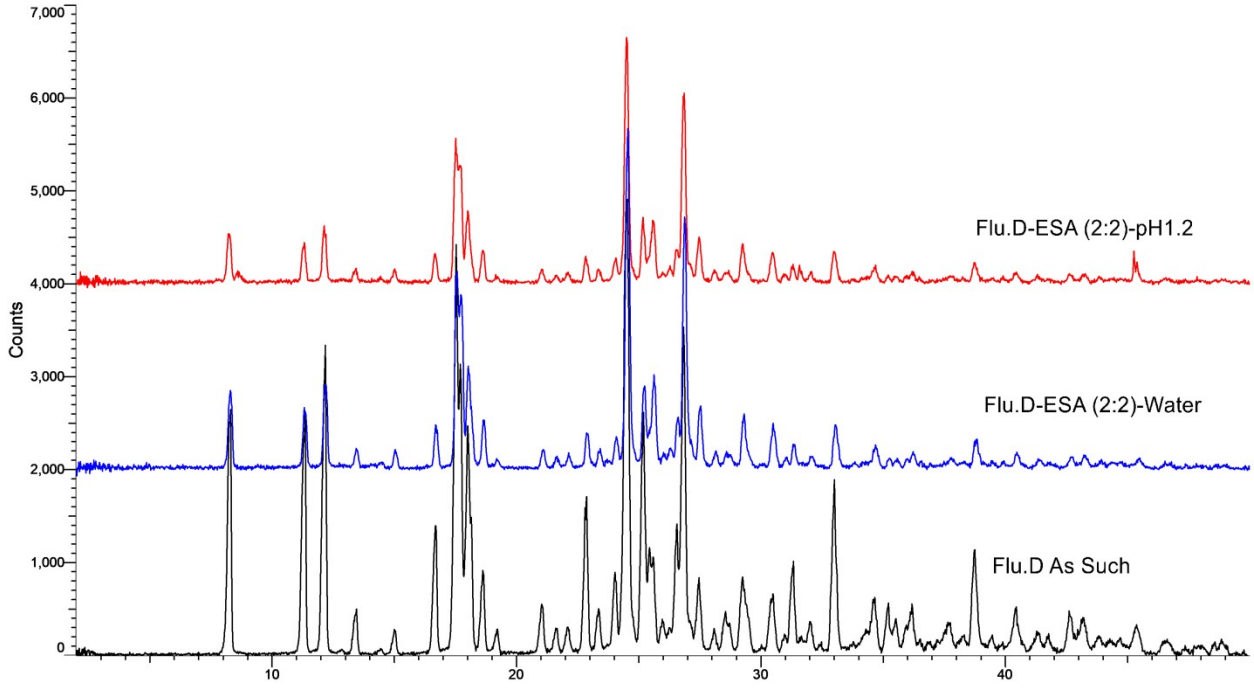

Figure S30. PXRD overlay of Flu.D with samples recovered after 24hrs solubility study in water (Flu.D-ESA (2:2)-Water) and pH 1.2 (Flu.D-ESA (2:2)-pH 1.2).

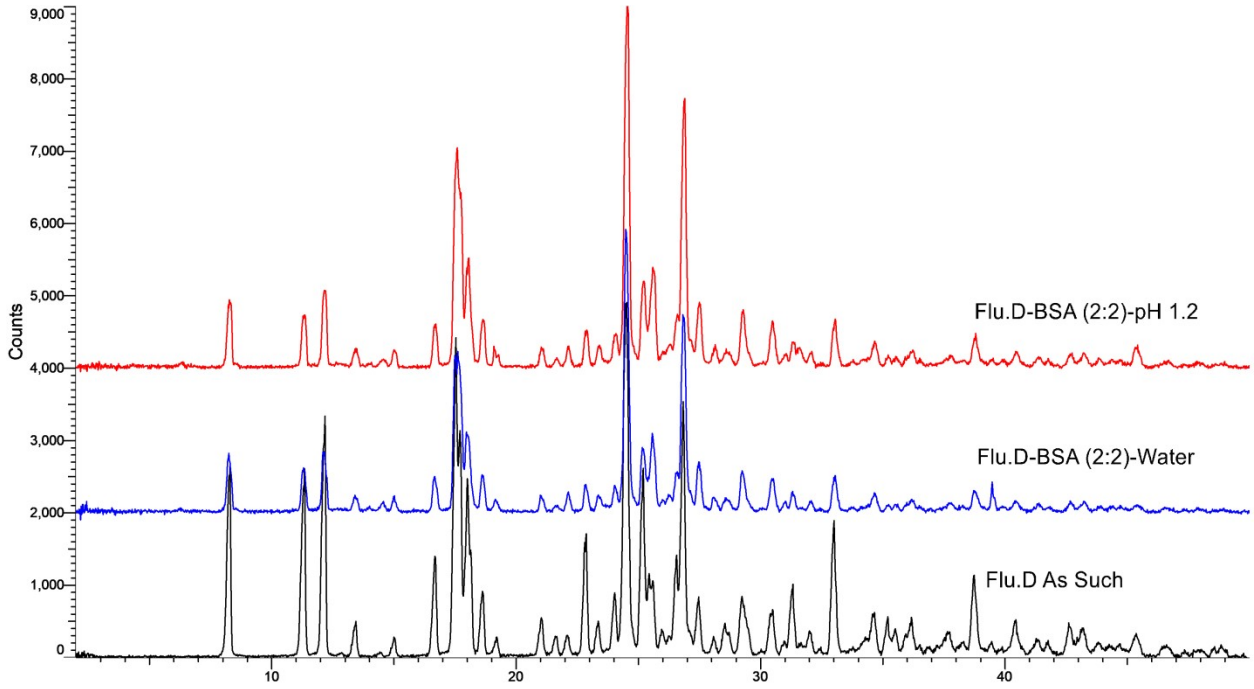

Figure S31. PXRD overlay of Flu.D with residues recovered after solubility study (24hr) in water (Flu.D-BSA (2:2)-Water) and pH 1.2 (Flu.D-BSA (2:2)-pH1.2).

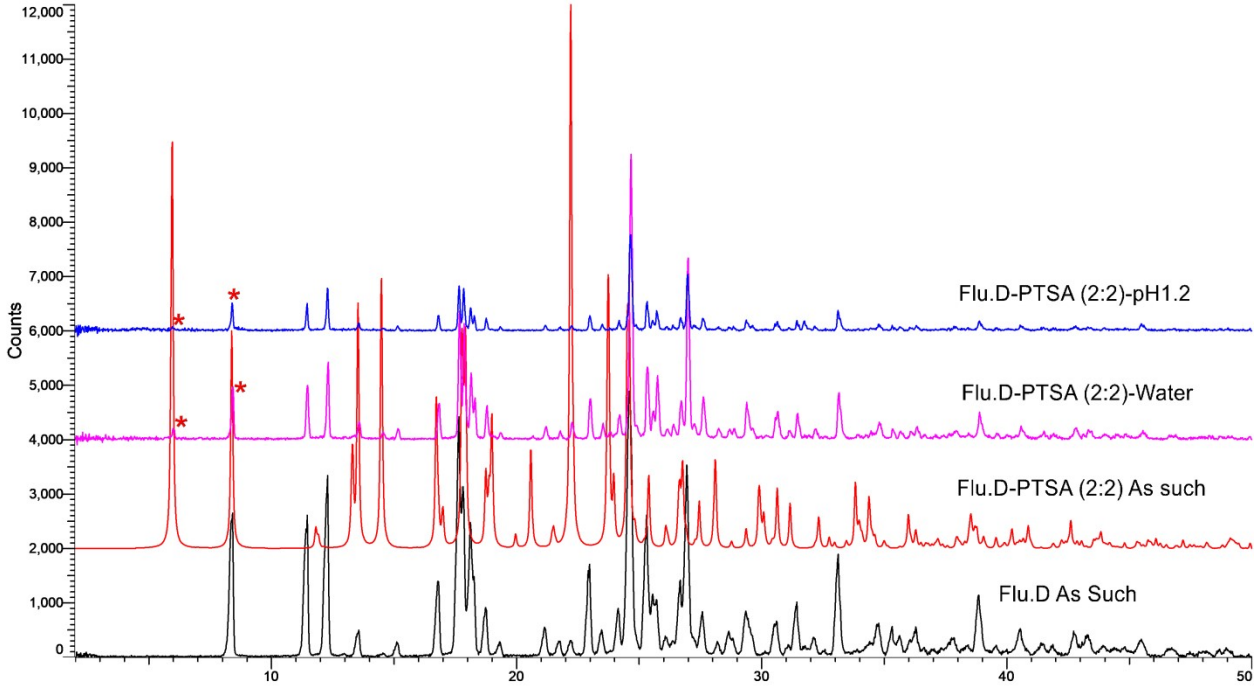

Figure S32. PXRD overlay of Flu.D, Flu.D-PTSA (2:2) with residues recovered after 24hr solubility study in water (Flu.D-PTSA (2:2)-Water) and pH 1.2 (Flu.D-PTSA (2:2)-pH1.2)).

Table S1. Crystallographic data and structure refinement parameters of the Flu.D salts.								
Compound	Flu.D-MSA (1:1)	Flu.D-MSA (2:2)	Flu.D-ESA (2:2)	Flu.D-BSA (1:1)	Flu.D-BSA(2:2)	Flu.D-BSA(6:6)	Flu.D-PTSA (2:2)	Flu.D-PTSA-H_2O (1:2:3)
Chemical formula	$C_7H_6F_3N_2O_2^+ \cdot CH_3O_3S^-$	$C_7H_6F_3N_2O_2^+ \cdot CH_3O_3S^-$	$C_7H_6F_3N_2O_2^+ \cdot C_2H_5O_3S^-$	$C_7H_6F_3N_2O_2^+ \cdot C_6H_5O_3S^-$	$C_7H_6F_3N_2O_2^+ \cdot C_6H_5O_3S^-$	$C_7H_6F_3N_2O_2^+ \cdot C_6H_5O_3S^-$	$C_7H_6F_3N_2O_2^+ \cdot C_7H_7O_3S^-$	$C_7H_6F_3N_2O_2^+ \cdot 2(C_7H_7O_3S^-).2(H_2O) \cdot H_3O^+$
CCDC number	2386899	2386905	2386904	2386900	2386902	2386906	2386901	2386903
M_r	302.23	302.23	316.26	364.30	364.30	364.30	378.32	604.57
Crystal system, space group	Monoclinic, *C*2/*c*	Monoclinic, *Cc*	Monoclinic, $P2_1/c$	Monoclinic, $P2_1$	Orthorhombic, $Pca2_1$	Triclinic, *P*1	Orthorhombic, $Pca2_1$	Monoclinic, $P2_1$
Temperature (K)	100 (2)							
a, *b*, *c* (Å)	21.4337 (18), 10.5337 (9), 12.9683 (12)	10.6002 (7), 10.6466 (7), 20.3303 (19)	12.9132 (14), 10.6737 (11), 18.342 (2)	7.4154 (4), 7.5301 (4), 13.6961 (7)	27.3846 (4), 7.4463 (8), 14.8172 (17)	7.4616 (17), 21.345 (4), 27.575 (6)	29.2994 (2), 7.4757 (5), 14.7336 (10)	9.8176 (6), 7.4895 (4), 17.8098 (10)
α, β, γ (°)	125.723 (4)	90.123 (4)	92.616 (5)	100.749 (2)		94.444 (5), 93.278 (6), 94.635 (6)		94.428 (3)

V (Å^3)	2377.0 (4)	2294.4 (3)	2525.4 (5)	751.35 (7)	3021.4 (5)	4355.3 (15)	3227.2 (3)	1305.63 (13)
Z	8	8	8	2	8	12	8	2
Radiation type	Mo $K\alpha$	Mo $K\alpha$	Mo $K\alpha$	Mo $K\alpha$	Mo $K\alpha$	Mo $K\alpha$	Mo $K\alpha$	Mo $K\alpha$
μ (mm^{-1})	0.33	0.34	0.32	0.28	0.28	0.29	0.26	0.29
Crystal size (mm)	0.31 × 0.29 × 0.21	0.31 × 0.25 × 0.20	0.31 × 0.29 × 0.21	0.31 × 0.29 × 0.26	0.25 × 0.21 × 0.19	0.30 × 0.26 × 0.23	0.31 × 0.29 × 0.27	0.31 × 0.25 × 0.20
Data collection								
Diffractometer	Bruker D8 QUEST PHOTON-100							
Absorption correction	Multi-scan *SADABS* 2016/2: Krause, L., Herbst-Irmer, R., Sheldrick G.M. & Stalke D., J. Appl. Cryst. 48 (2015) 3-10							
T_{min}, T_{max}	0.609, 0.745	0.689, 0.746	0.631, 0.746	0.664, 0.746	0.587, 0.746	0.679, 0.746	0.668, 0.746	0.513, 0.746
No. of measured, independent and observed [$I > 2\sigma(I)$] reflections	10245, 2418, 1817	57350, 6971, 6919	37253, 6341, 3851	12793, 4509, 4347	44903, 7806, 6784	162486, 26455, 16622	27143, 8872, 7791	34218, 6462, 4546
R_{int}	0.038	0.040	0.071	0.026	0.036	0.069	0.028	0.108
$(\sin\theta/\lambda)_{max}$ (Å^{-1})	0.626	0.717	0.670	0.716	0.715	0.716	0.714	0.668
Refinement								
$R[F^2 > 2\sigma(F^2)]$, $wR(F^2)$, S	0.036, .087, 1.03	0.031, 0.081,	0.044, 0.122,	0.028, 0.070,	0.036, 0.081,	0.044, 0.117,	0.033, 0.073, 1.02	0.056, 0.115, 1.01

		1.16	1.01	1.06	1.06	1.02		
No. of reflections	2418	6971	6341	4509	7806	26455	8872	6462
No. of parameters	185	370	387	229	457	1369	477	387
No. of restraints		3		1	1		1	10
H-atom treatment	H atoms treated by a mixture of independent and constrained refinement							
$\Delta\rho_{max}$, $\Delta\rho_{min}$ (e Å^{-3})	0.28, −0.36	0.44, −0.31	0.52, −0.50	0.33, −0.24	0.55, −0.36	0.74, −0.55	0.27, −0.28	0.61, −0.52
Absolute structure		Refined as an inversion twin.		Flack x determined using 1933 quotients [(I+)-(I-)]/[(I+)+(I-)] (Parsons, Flack and Wagner, Acta Cryst. B69 (2013) 249-	Flack x determined using 2368 quotients [(I+)-(I-)]/[(I+)+(I-)] (Parsons, Flack and Wagner, Acta Cryst. B69 (2013) 249-259).		Flack x determined using 3166 quotients [(I+)-(I-)]/[(I+)+(I-)] (Parsons, Flack and Wagner, Acta Cryst. B69 (2013) 249-259).	Flack x determined using 1488 quotients [(I+)-(I-)]/[(I+)+(I-)] (Parsons, Flack and Wagner, Acta Cryst. B69 (2013) 249-259).

				259).				
Absolute structure parameter		0.07 (7)		0.009 (19)	0.007 (18)		0.03 (2)	0.06 (5)

Table S2. Hydrogen bond geometries of Flu.D salts

D—H···*A*	*D*—H (Å)	H···*A* (Å)	*D*···*A* (Å)	*D*—H···*A* (°)
Flu.D-MSA (1:1)				
N2—H2*NB*···O5	0.89 (3)	1.91 (3)	2.739 (3)	154 (2)
N2—H2*NC*···O3^{i}	0.96 (3)	1.79 (3)	2.734 (2)	168 (2)
N2—H2*NA*···O4^{ii}	0.91 (3)	1.90 (3)	2.792 (3)	166 (2)
Symmetry codes: (i) −*x*+1/2, −*y*+3/2, −*z*+1; (ii) *x*, −*y*+1, *z*−1/2				
Flu.D-MSA (2:2)				
N2*B*—H2*ND*···O3*B*	0.90 (4)	1.88 (4)	2.777 (3)	175 (4)
N2*A*—H2*NB*···O5*A*	0.85 (4)	2.10 (4)	2.902 (3)	157 (4)
N2*A*—H2*NC*···O5*B*	0.90 (2)	1.89 (2)	2.770 (3)	169 (6)
N2*A*—H2*NA*···O3*A*^{i}	0.81 (5)	2.02 (5)	2.829 (3)	172 (5)
N2*B*—H2*NF*···O5*B*^{i}	0.82 (4)	2.14 (4)	2.911 (3)	158 (4)
N2*B*—H2*NE*···O5*A*^{ii}	0.90 (5)	1.89 (5)	2.775 (3)	167 (4)
Symmetry codes: (i) *x*−1/2, *y*−1/2, *z*; (ii) *x*, *y*−1, *z*				
Flu.D-ESA (2:2)				
N2*A*—H2*NA*···O3*B*	0.98 (3)	1.72 (3)	2.704 (3)	179 (3)
N2*A*—H2*NB*···O5*A*	0.93 (3)	1.85 (3)	2.714 (3)	153 (2)

N2*B*—H2*NE*···O5*B*	0.86 (3)	1.93 (3)	2.741 (3)	157 (2)
N2*B*—H2*ND*···O4*A*	0.92 (3)	1.78 (3)	2.704 (3)	175 (3)
N2*A*—H2*NC*···O4*B*^{i}	0.91 (3)	1.91 (3)	2.790 (3)	163 (2)
N2*B*—H2*NF*···O3*A*^{ii}	0.89 (3)	1.95 (3)	2.816 (3)	165 (3)
Symmetry codes: (i) −*x*, *y*+1/2, −*z*+3/2; (ii) −*x*+1, *y*−1/2, −*z*+3/2.				
Flu.D-BSA (1:1)				
N2—H2*NB*···O5	1.00 (3)	1.74 (3)	2.738 (2)	174 (3)
N2—H2*NA*···O3^{i}	0.90 (3)	1.88 (3)	2.778 (2)	172 (3)
N2—H2*NC*···O3^{ii}	0.91 (3)	2.16 (3)	2.865 (2)	134 (2)
N2—H2*NC*···O4^{iii}	0.91 (3)	2.18 (3)	2.870 (2)	132 (2)
Symmetry codes: (i) −*x*+1, *y*−1/2, −*z*; (ii) *x*−1, *y*, *z*; (iii) −*x*+1, *y*+1/2, −*z*.				
Flu.D-BSA (2:2)				
N2*A*—H2*NC*···O3*A*	0.88 (4)	2.30 (3)	2.897 (3)	124 (3)
N2*A*—H2*NA*···O3*B*	0.89 (3)	1.85 (3)	2.734 (3)	173 (3)
N2*B*—H2*NE*···O5*B*	0.88 (4)	1.88 (4)	2.724 (3)	161 (4)
N2*B*—H2*NF*···O4*A*	0.96 (3)	1.86 (3)	2.799 (3)	164 (3)
N2*A*—H2*NC*···O5*B*^{i}	0.88 (4)	2.07 (4)	2.877 (3)	150 (3)
N2*A*—H2*NB*···O5*A*^{ii}	0.94 (4)	1.84 (4)	2.757 (3)	166 (3)
N2*B*—H2*ND*···O5*A*^{iii}	0.90 (3)	2.03 (3)	2.863 (3)	155 (3)
Symmetry codes: (i) *x*, *y*+1, *z*; (ii) −*x*+3/2, *y*, *z*+1/2; (iii) *x*, *y*−1, *z*.				
Flu.D-BSA (6:6)				
N2*A*—H2*NA*···O4*B*	0.89 (2)	1.88 (2)	2.751 (2)	168 (2)
N2*A*—H2*NB*···O5*A*	0.92 (2)	2.07 (2)	2.895 (2)	148.7 (19)

N2*B*—H2*NE*···O3*B*	0.90 (3)	1.89 (3)	2.778 (2)	170 (2)
N2*C*—H2*NG*···O3*C*	0.93 (2)	1.85 (2)	2.770 (2)	171.2 (19)
N2*C*—H2*NH*···O4*A*	0.88 (2)	1.99 (2)	2.845 (2)	164 (2)
N2*C*—H2*NI*···O5*D*	0.86 (2)	2.30 (2)	2.826 (2)	120.0 (18)
N2*D*—H2*NK*···O4*C*	0.93 (2)	1.82 (2)	2.746 (2)	171.4 (19)
N2*D*—H2*NL*···O3*D*	0.89 (3)	1.96 (3)	2.846 (2)	171 (2)
N2*E*—H2*NM*···O3*F*	0.89 (3)	1.89 (3)	2.754 (2)	163 (2)
N2*E*—H2*NO*···O4*E*	0.92 (2)	2.58 (2)	3.161 (2)	122.1 (17)
N2*E*—H2*NO*···O5*E*	0.92 (2)	1.88 (2)	2.745 (2)	156.5 (19)
N2*F*—H2*NP*···O4*E*	0.92 (2)	1.85 (2)	2.753 (2)	169 (2)
N2*F*—H2*NQ*···O5*F*	0.90 (2)	2.06 (2)	2.874 (2)	149.0 (19)
N2*A*—H2*NC*···O4*A*^{i}	0.93 (2)	1.93 (2)	2.849 (2)	167.6 (19)
N2*B*—H2*ND*···O3*D*^{i}	0.91 (2)	1.97 (3)	2.839 (2)	160 (2)
N2*B*—H2*NF*···O3*A*^{i}	0.87 (2)	2.27 (2)	2.815 (2)	121.0 (19)
N2*B*—H2*NF*···O4*B*^{i}	0.87 (2)	2.31 (2)	2.990 (2)	135 (2)
N2*D*—H2*NJ*···O4*D*^{i}	0.86 (3)	2.16 (3)	2.937 (2)	149 (2)
N2*C*—H2*NI*···O4*C*^{ii}	0.86 (2)	2.34 (2)	3.006 (2)	135.1 (18)
N2*E*—H2*NN*···O4*F*^{iii}	0.88 (3)	2.09 (2)	2.858 (2)	146 (2)
Symmetry codes: (i) *x*+1, *y*, *z*; (ii) *x*−1, *y*, *z*; (iii) −*x*+3, −*y*+3, −*z*+2; (iv) *x*+1, *y*+1, *z*				
Flu.D-PTSA (2:2)				
N2*A*—H2*NB*···O5*A*	0.88 (3)	1.86 (3)	2.736 (2)	169 (3)
N2*B*—H2*ND*···O4*A*	1.00 (3)	1.76 (3)	2.740 (3)	167 (3)

N2*B*—H2*NE*···O5*B*	0.88 (3)	1.90 (3)	2.765 (3)	164 (3)
N2*A*—H2*NA*···O3*B*^{i}	0.94 (3)	1.89 (3)	2.803 (3)	164 (2)
N2*B*—H2*NF*···O4*B*^{i}	0.88 (3)	2.31 (3)	2.940 (3)	128 (2)
N2*A*—H2*NC*···O5*B*^{ii}	0.88 (3)	2.05 (3)	2.889 (3)	161 (2)
N2*B*—H2*NF*···O5*A*^{iii}	0.88 (3)	2.11 (3)	2.892 (3)	148 (2)
Symmetry codes: −*x*+3/2, *y*, *z*+1/2; (ii) −*x*+3/2, *y*−1, *z*+1/2; (iii) *x*, *y*+1, *z*				
Flu.D-PTSA-H_2O (1:2:3)				
N2—H2*NA*···O5*A*^{i}	0.86 (6)	2.10 (6)	2.904 (6)	155 (5)
N2—H2*NB*···O3*B*^{i}	0.97 (7)	1.80 (7)	2.745 (6)	163 (6)
N2—H2*NC*···O3*A*	0.84 (7)	2.07 (7)	2.797 (6)	145 (6)
O1*W*—H1*W*···O3*A*	0.89 (3)	1.85 (3)	2.740 (5)	175 (6)
O1*W*—H2*W*···O3*B*	0.85 (3)	1.97 (3)	2.814 (5)	171 (6)
O2*W*—H3*W*···O5*B*	0.90 (2)	1.81 (3)	2.700 (5)	173 (4)
O2*W*—H4*W*···O1*W*^{iii}	0.88 (2)	1.73 (3)	2.602 (5)	168 (5)
O3*W*—H5*W*···O4*B*^{iv}	0.93 (3)	1.77 (3)	2.689 (5)	173 (5)
O3*W*—H6*W*···O4*A*^{v}	0.92 (3)	1.74 (3)	2.633 (5)	165 (5)
O3*W*—H7*W*···O2*W*	0.89 (2)	1.54 (2)	2.431 (5)	174 (5)
Symmetry codes: (i) *x*, *y*+1, *z,* (ii) *x*, *y*−1, *z,* (iii) −*x*, *y*−1/2, −*z*+1, (iv) −*x*+1, *y*−1/2, −*z*+1.				

Table.S3 Details of experiments conducted for flutamide using various coformers.

API	Coformer	Experiment	Result

Flutamide (20mg)	Adenine	Slow evaporation	Physical mixture
	Cytosine	Slurry	
	Thymine		
	Sorbic acid		
	Orotic acid		
	Uracil		
	2-Bromo benzoic acid		
	4-Chloro benzoic acid	Slow evaporation	
	Adipic acid		
	Ethenzamide		
	L-argenine		
	Pamoic acid		
	Theophylline		
	Saccharin		
	Caffeine		
	Maleic acid		

Flutamide (20mg)	DL tartaric acid	Slurry	Physical Mixture
	Nicotinic acid		
	Iso nicotinic acid	Slow evaporation	
	Succinic acid		
	Benzoic acid		
	Oxalic acid		
	Paracetamol		
	Phenacitin		
	Imidazole	Slurry	
	Taurine		
	Camphor sulfonic acid		
	L-proline		
	2,2′-Bipyridine		
	4-Amino benzoic acid		
Flutamide(20mg)	Imidazole		Physical Mixture
	DL-tartaric acid		

Table S4. Degradation profile of flutamide. Rt indicates retention time			
Standard	Rt Time (min)	Drug Percentage (%)	
		Flutamide	Flu.D
Flutamide standard	5.5	100	0
Acid	4.9	0	10.05
Base	4.9	0	2.4
Neutral	5.5	97.13	2.86
3%H_2O_2	5.5	100	0
Photolytic	5.5	100	0
Thermal	5.5	100	0

Table S5. DSC observation of the Flu.D salts				
Compound	Initial endotherm		Final melting endotherm	
	T_{Onset}(°C)	T_{Peak}(°C)	T_{Onset}(°C)	T_{Peak}(°C)
Flutamide	-	-	111.29	113.76
Flu.D	-	-	126.66	128.63
Flu.D-MSA (1:1)	123	126.21	174.2	175.63
Flu.D-BSA (2:2)	177.24	183.65	222.16	223.43
Flu.D-PTSA (2:2)	174.8	178.27	215.19	216.16
Flu.D-ESA (2:2)	-	-	142.66	143.96

Table S6. Cumulative drug release profiles at specified intervals of time in water media.						
Time Interval (minutes)	% Cumulative drug release of					
	Flutamide	Flu.D	Flu.D-MSA (1:1)	Flu.D-ESA (2:2)	Flu.D-BSA (2:2)	Flu.D-PTSA (2:2)
0	0	0	0	0	0	0
1	2	0.31	3.7	2.3	7.5	11
5	3.2	3.1	18.8	10.8	22.5	32.3

10	4.1	7.2	30.5	20.3	35.9	50.7
20	5.4	14	45.9	34.1	50.8	71.1
40	9.1	25.7	58.5	49.9	68.2	87.1
80	14.1	37.3	69.4	70.2	81.3	93.9
120	23.2	45.7	76.5	81.5	88.4	96.2

Table S7. Cumulative drug release profiles at specified intervals of time in pH 1.2 media.

Time Interval (minutes)	**% Cumulative drug release of**					
	Flutamide	**Flu.D**	**Flu.D-MSA (1:1)**	**Flu.D-ESA (2:2)**	**Flu.D-BSA (2:2)**	**Flu.D-PTSA (2:2)**
0	0	0	0	0	0	0
1	3.5	0.43	6.3	1.2	6.3	10.7
5	5.1	0.49	30.5	16.3	25.9	29.5
10	5.8	4.6	44.3	28.9	41.9	47.9
20	7.6	11	56.9	46.4	60.1	67.8
40	10.4	20.1	69.6	66.1	77.3	86
80	15.4	30.9	75.5	81.8	87.2	95
120	25.6	38.7	82.9	87.2	92.6	97.2