Electronic Supplementary Material (ESI) for CrystEngComm.

Mechanochemical screening of drug-drug eutectics of the antibacterial agent, linezolid

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Supporting Information

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Experimental details

Materials:

The APIs are purchased from various suppliers, and used without further purification. The HPLC grade methanol from Merck (99.9% pure) was used for liquid-assisted grinding.

Mechanochemical Synthesis by LAG:

For the preparation of solid forms performing LAG with methanol using LABINDIA MM1100 Micro Ball Mill. All the drug-drug combinations were prepared using the mechanochemical route in various stoichiometric ratios. For every LAG experiment, maintained the η value (solvent/solute) ranges between ~ 0.1- 0.5 μL/ mg.

The LABINDIA micro ball mill is equipped with a 5 mL stainless steel jar and one 7 mm diameter grinding ball per jar milled at 900 rpm (15 Hz) for 30 min (3 cycles of 10 min). The resultant powder was analysed using PXRD and melting point to confirm whether it is a molecular complex or eutectic mixture.

Differential Scanning Calorimetry (DSC):

DSC thermogram acquired using a METTLER TOLEDO DSC (STARe system) unit. using 40 μL aluminium crucibles with approximately 5-7 mg of the sample under a dynamic nitrogen atmosphere (40 mL/min) and a heating rate of 10 ºC/min in the temperature range from 60 to 200ºC.

Optical and Hot-Stage Microscope (HSM):

Based on the thermal information from the optical and Hot-Stage Microscope (HSM) studies, we constructed the phase diagram to determine the eutectic point**.** The binary phase diagrams correlate the melting temperatures of different drug compositions with respect to the mole fraction of LZD.

Powder X-ray Diffraction (PXRD)

On a Philips X' pert Pro with Cu K radiation (1.54056) at room temperature, we measured the diffractions experiments for the drug-drug combinations at varying stoichiometric proportions. Further, we collected the diffraction data of the materials post-dissolution (after 24 hours) to determine their phase stability.

That is LZD-HAD, LZD-ASA, LZD-IND, LZD-PHE, LZD-OSB, LZD-SMX, and, LZD-STZ, in 1:1,2:1,2:3,3:7,1:1,1:1, and, 2:1 respectively.

Scanning Electron Microscopy (SEM):

Micrographs were obtained using a Hitachi Tabletop JEOL 5600 SL scanning electron microscope operated in the range of 5–30 kV. The samples were prepared by drop casting on silicon wafer pasted in a carbon double-sided adhesive tape fixed on the sample holder.

Fourier-Transform Infrared Spectroscopy* (*FTIR):

On a PerkinElmer Attenuated Total Reflectance (ATR) instrument, recorded Fourier transform infrared (FTIR) spectra at atmospheric conditions with a resolution of 4 cm^{-1} and 32 scans. All samples used in data collection were in the form of solid powders and spectra were recorded in the wavenumber range 400−4000 cm^{-1}.

Solubility studies:

We assessed the solubility of drug-drug eutectic combinations in distilled water using pelletized samples obtained by compressing using a hydraulic press at a total force of 75 kg/cm^2. The pellet shook continuously for 24 hours at a speed of 100 rpm using an orbital benchtop shaker and the absorbance value was measured at 250 nm using a Shimadzu UV-1800 spectrophotometer. After 24 hours shaking, the slurry was separated as the residual of the solubility test for the stability confirmation studies.

Dissolution studies:

The dissolution tests of pelletized (75 kg/cm^2) samples were carried out using the USP paddle method on a Microprocessor Dissolution test apparatus (Make: ESICO International, India). Each test used 900 mL of pH 6.8 phosphate buffer as the dissolution medium. The stirring speed was set to 75 rpm and the temperature was kept constant at 37 °C. In the dissolution medium, accurately weighed samples containing the 300 mg eutectic mixture and added 2.5% sodium starch glycolate. After 30 minutes, about 1 mL of solution was withdrawn and filtered with a syringe filter. HPLC was used to calculate the percentage of drug availability.

High-Performance Liquid Chromatography (HPLC) Analysis:

HPLC analysis was conducted on a Shimadzu LC-20AD HPLC system with a UV detection of 250 nm using a C18 column (Phenomenex 5 μm × 4.6 mm × 250 mm column). The column temperature was set to 35 °C. The mobile phase consisted of a mixture of methanol and water solution 50% (v/v). The isocratic elution was used with a flow rate of 1 mL/min. We performed HPLC analysis on dissolution sample and pure drug (for preparing standared curve). Utilizing the standard curve of each, we determined the percentage availability of both LZD and coformer drugs.

Computational studies

By extracting CSD search, we gathered the LZD and coformer's recorded crystal structure. Before running the DFT calculations hydrogen atom positions in the cluster were normalized according to the standard neutron X-H bond lengths. Using the B3LYP hybrid density functional theory model, the conformational energies of the LZD were computed in Gaussian 16. For all atoms, used 6-311+ +g(d,p) basis set. and calculated the relative energy to optimise the stable conformation of the LZD among the three polymorphs. To demonstrate the likelihood of the creation of a eutectic mixture rather than a cocrystal, we used a variety of virtual cocrystal screening techniques, including the molecular complementarity tool (MCT), molecular electrostatic potential surface **(**MESP), and crystal structure prediction (CSP).

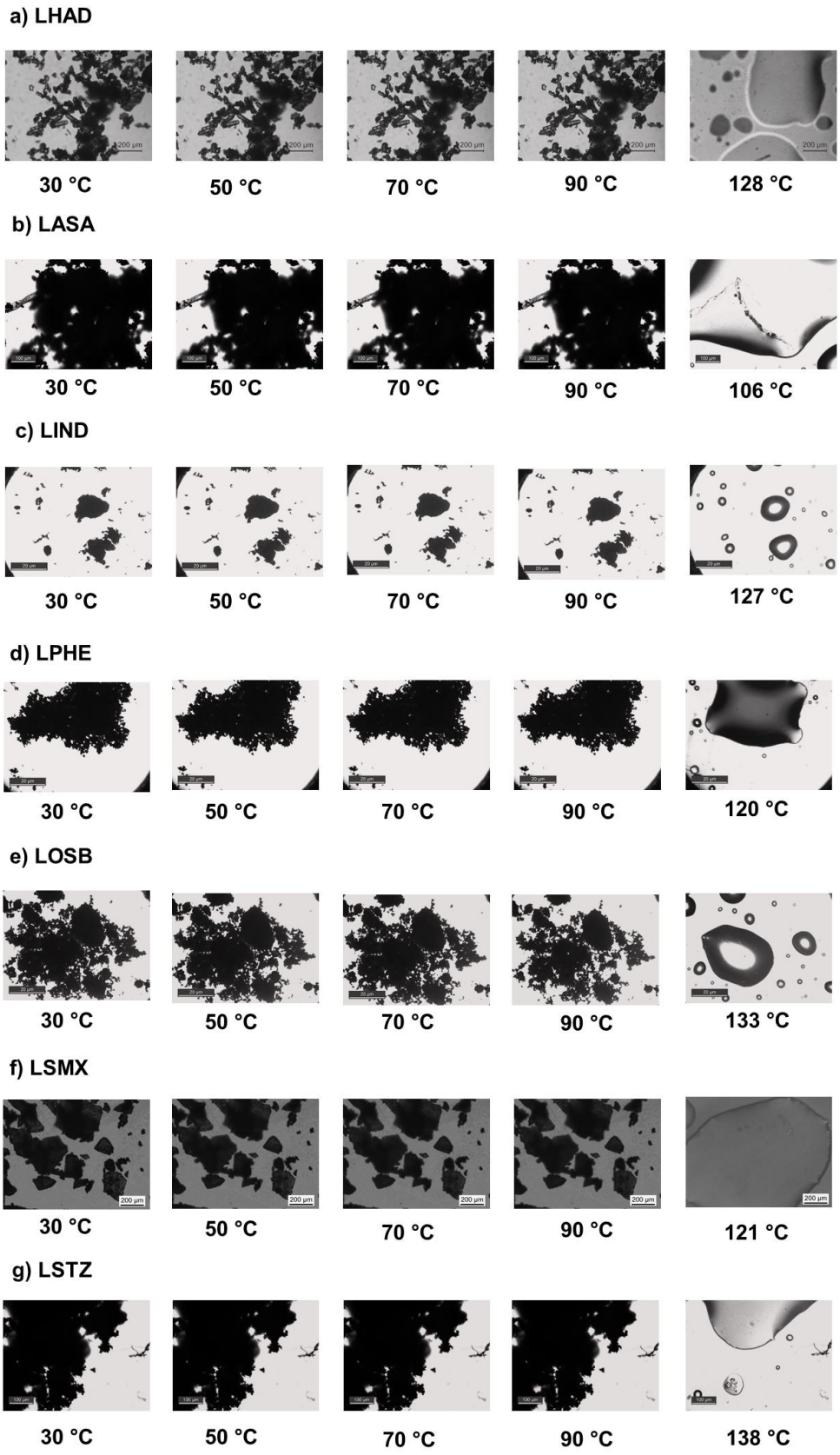


Fig. S1 Hot stage microscopic images of the eutectic composits.

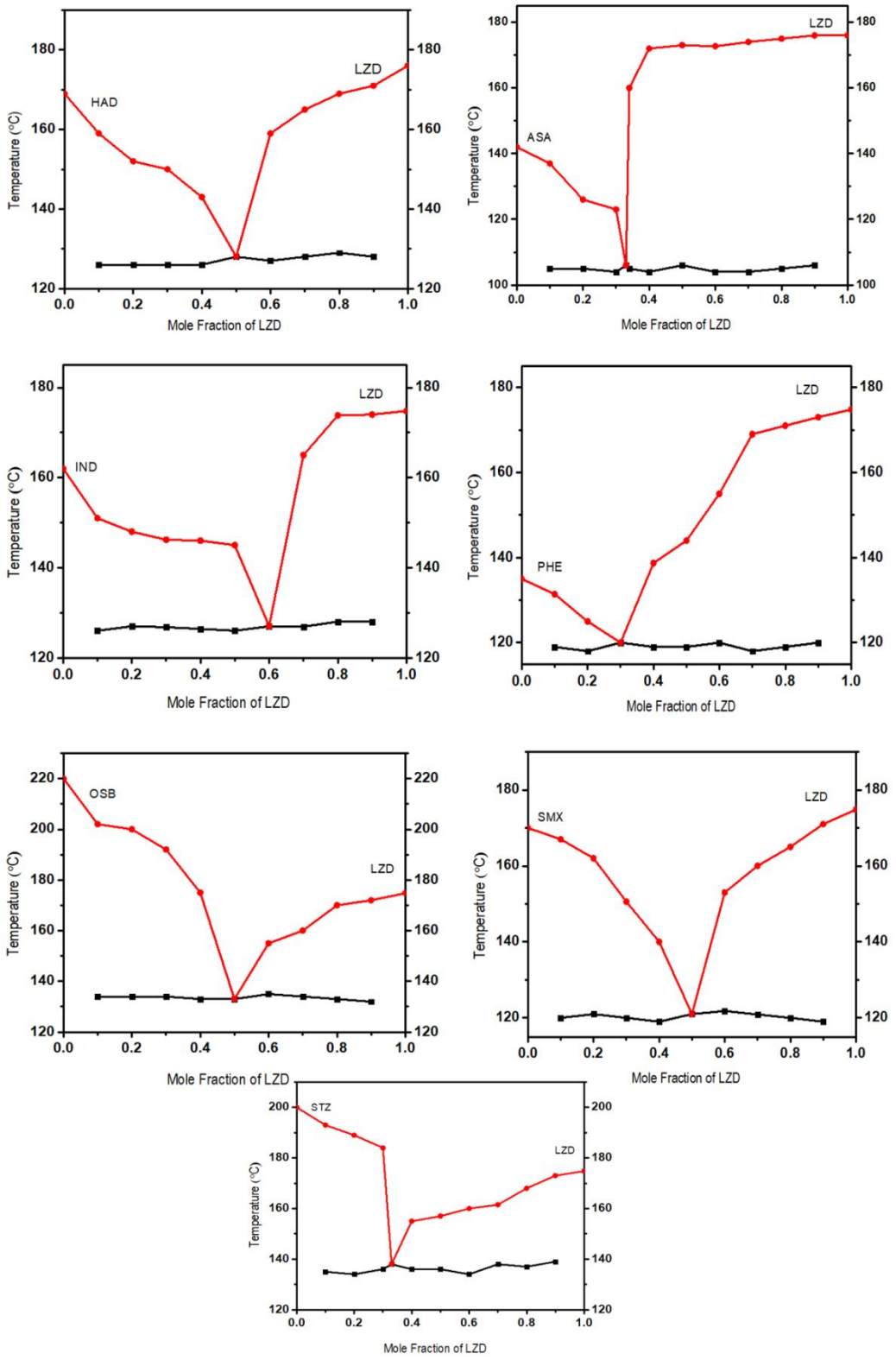
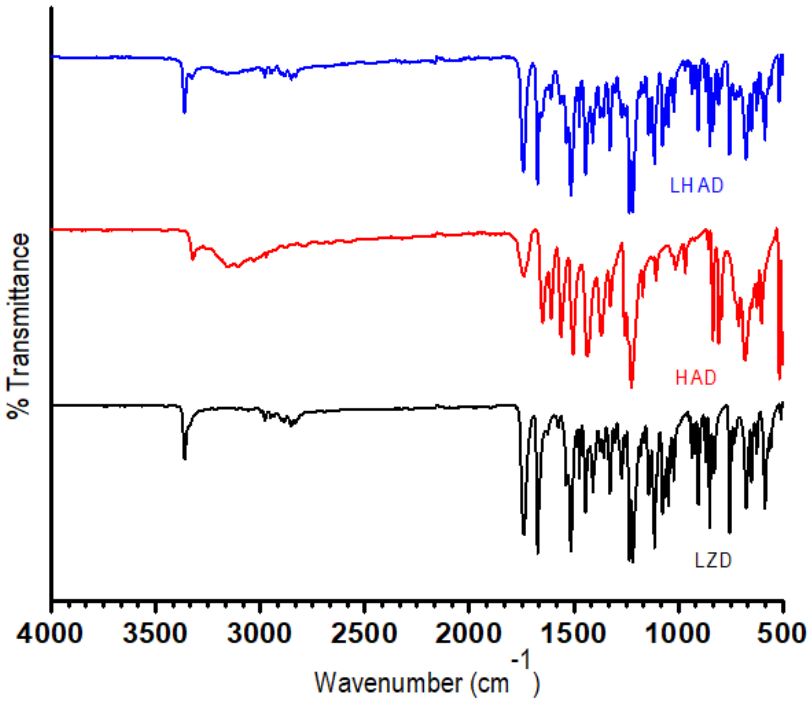


Fig. S2 Binary phase diagram of the eutectics of LZD with HAD, ASA, IND, PHE, OSB, SMX, and STZ. Solidus points are represented as black squares and liquidus points as red circles.



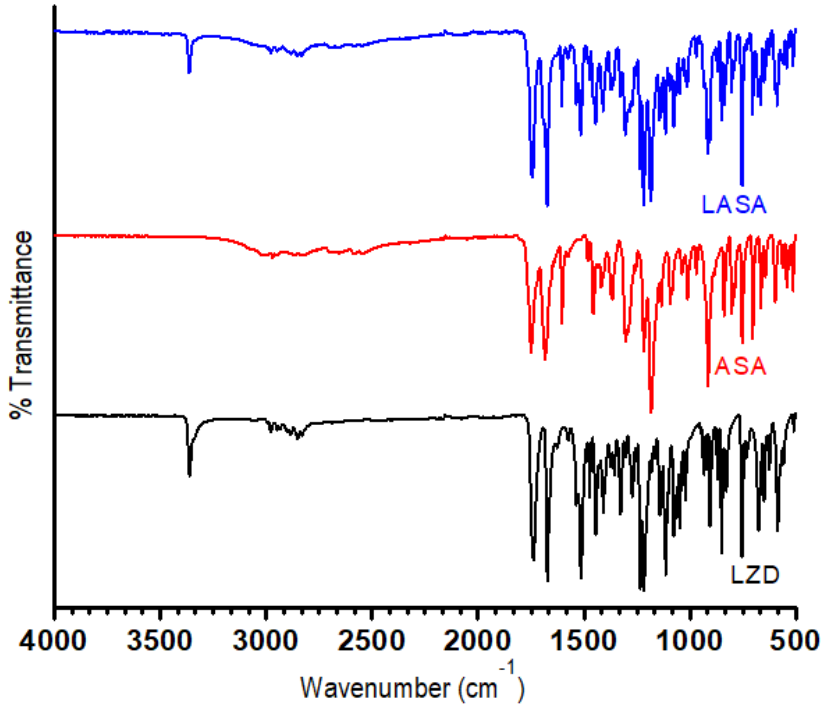


Fig. S3 IR Spectra of the eutectics of LZD with HAD, ASA

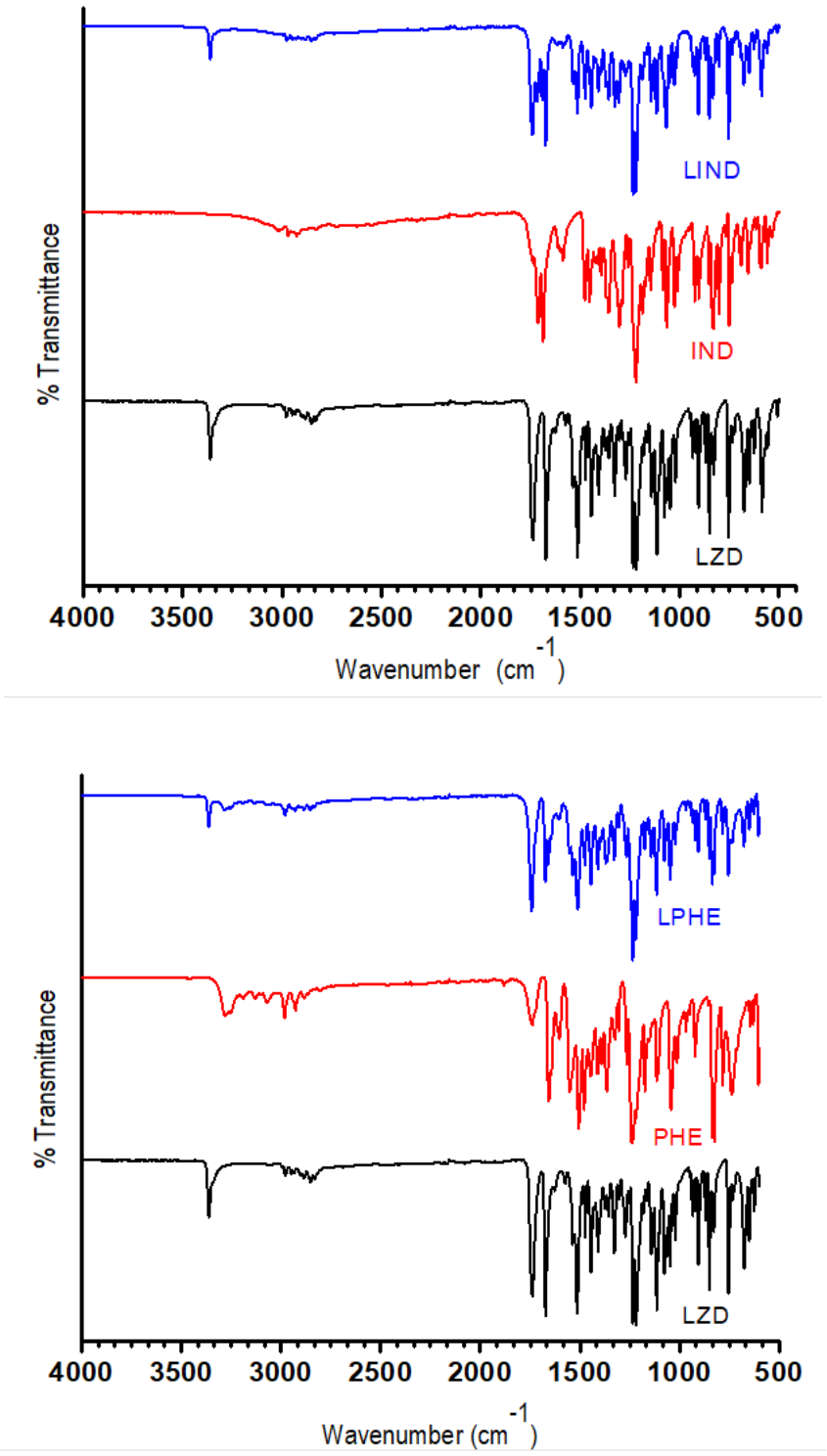


Fig. S3 (Contd.) IR Spectra of the eutectics of LZD with IND, PHE.

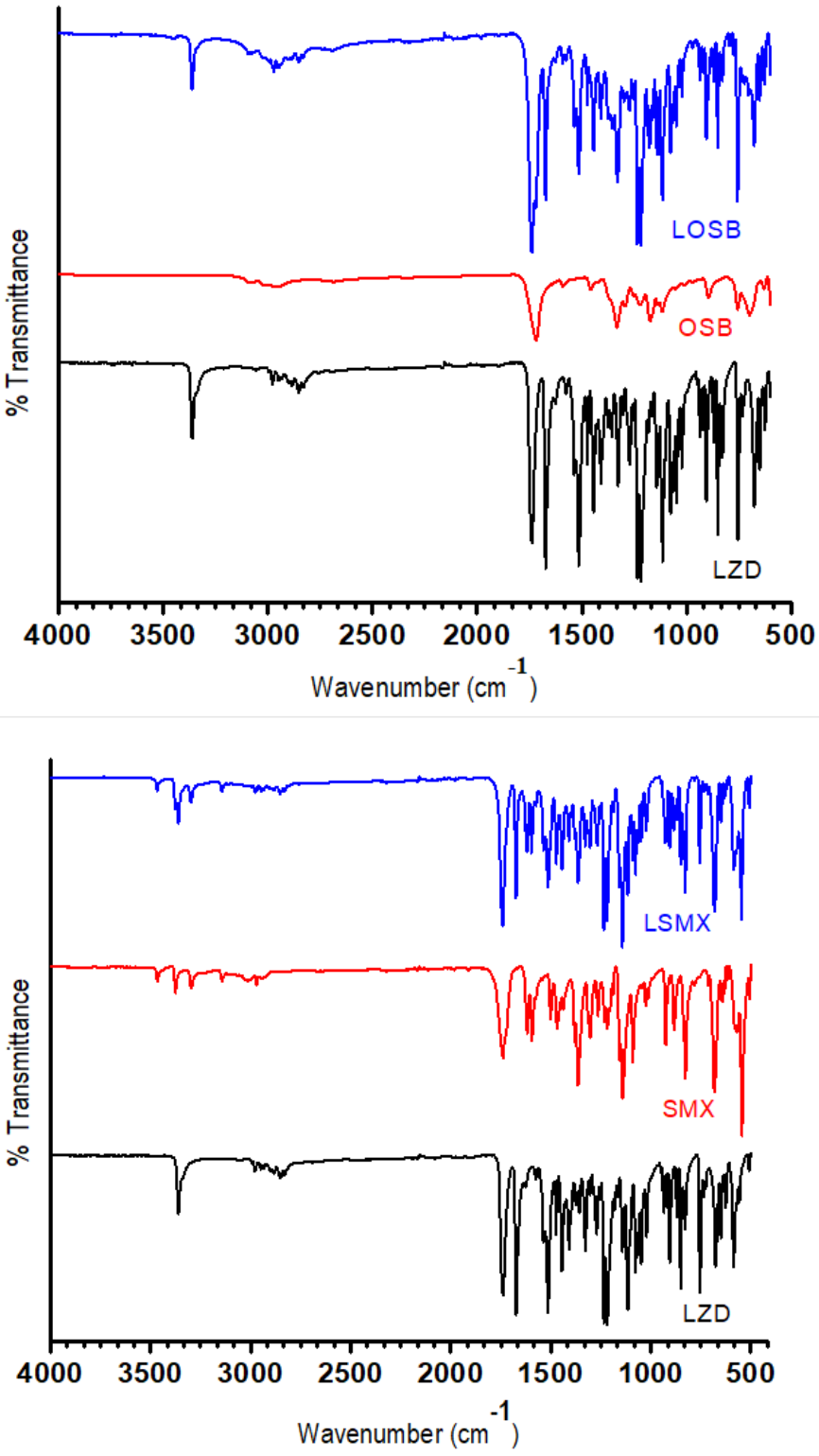


Fig. S3 (Contd.) IR Spectra of the eutectics of LZD with OSB, SMX.

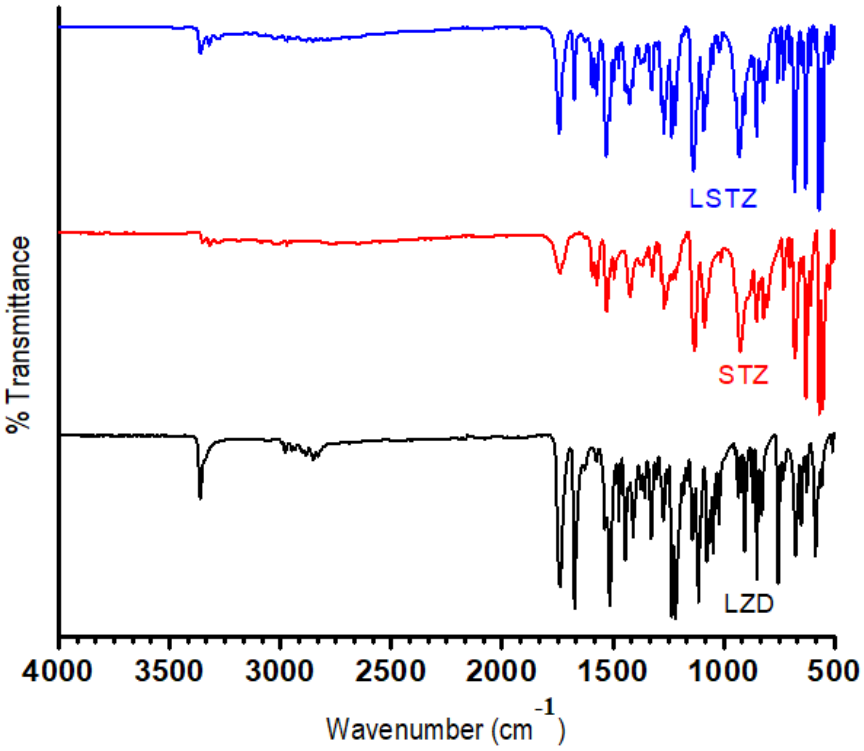


Fig. S3 (Contd.) IR Spectra of the eutectics of LZD with STZ.

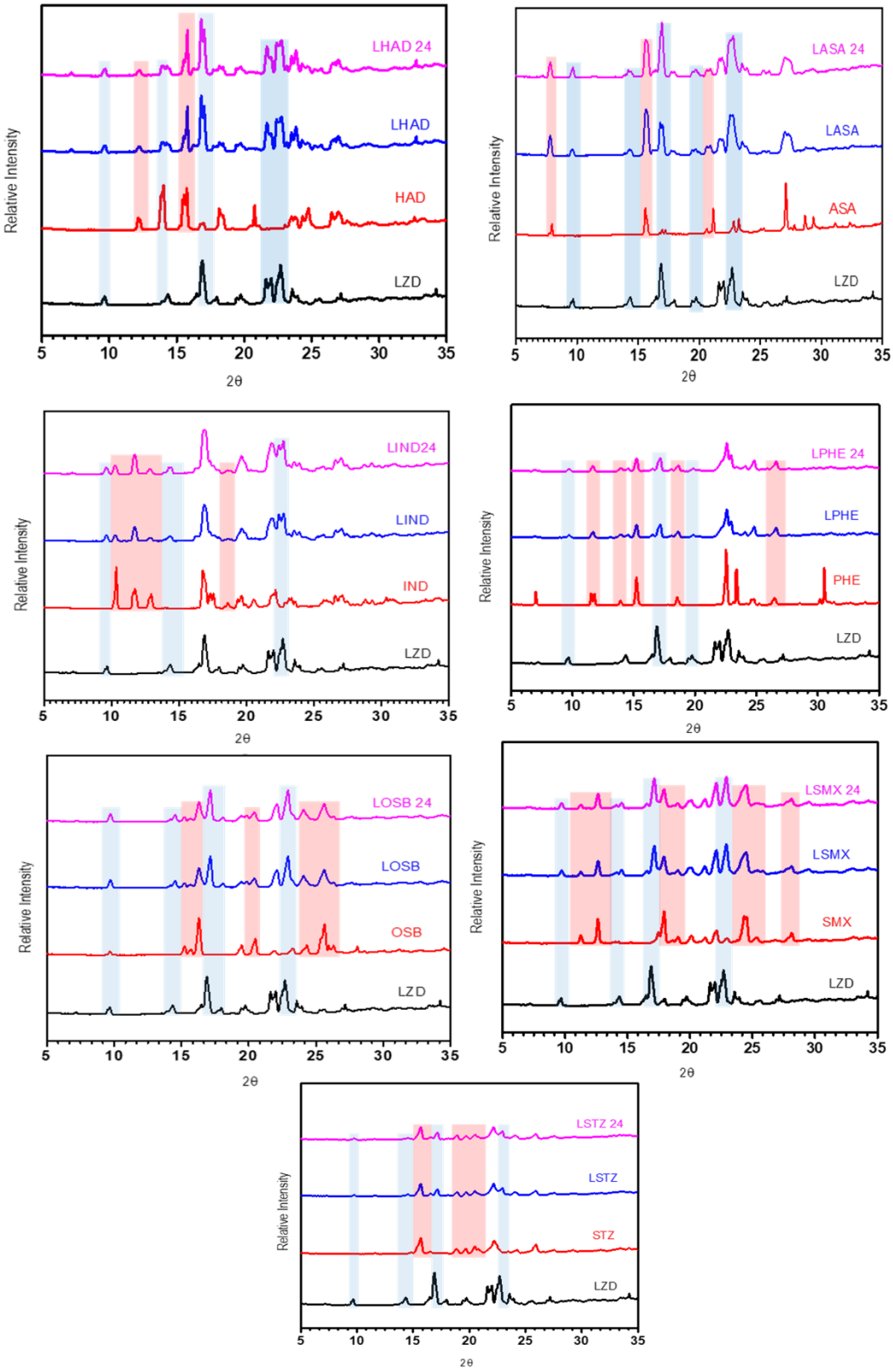


Fig. S4 PXRD pattern of the parent drug, drug-drug eutectics, and eutectic composite equilibrated for 24 hours.

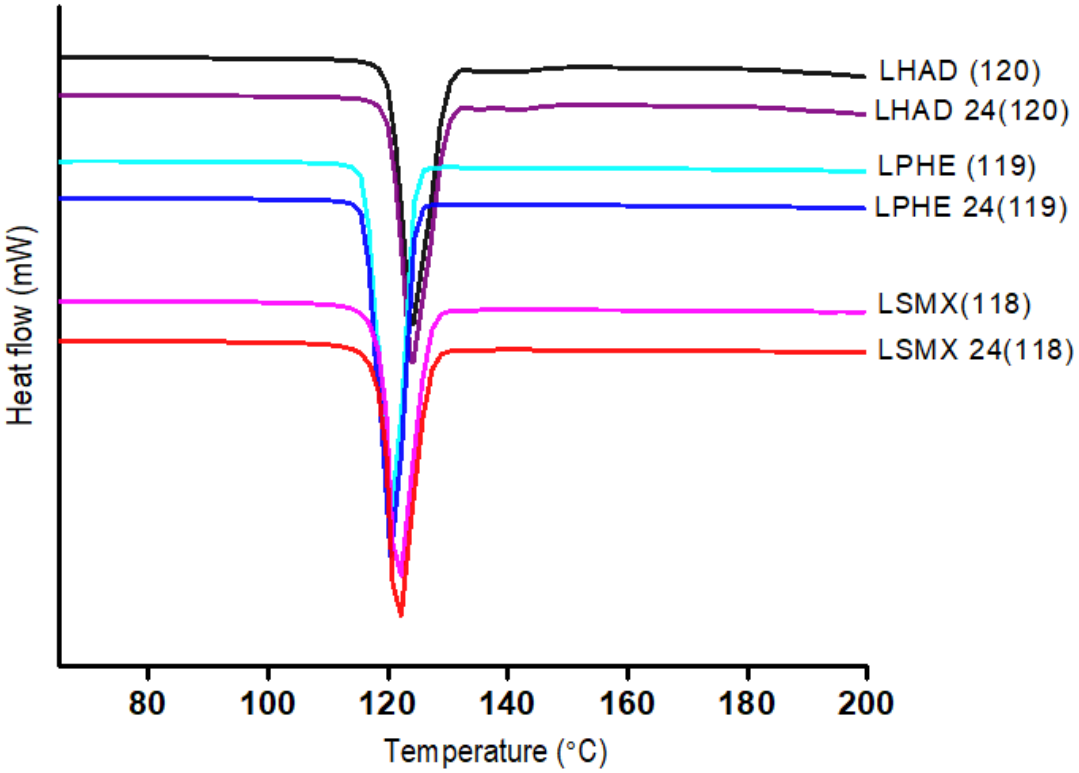


Fig. S5 DSC of the eutectics after 24 hrs.

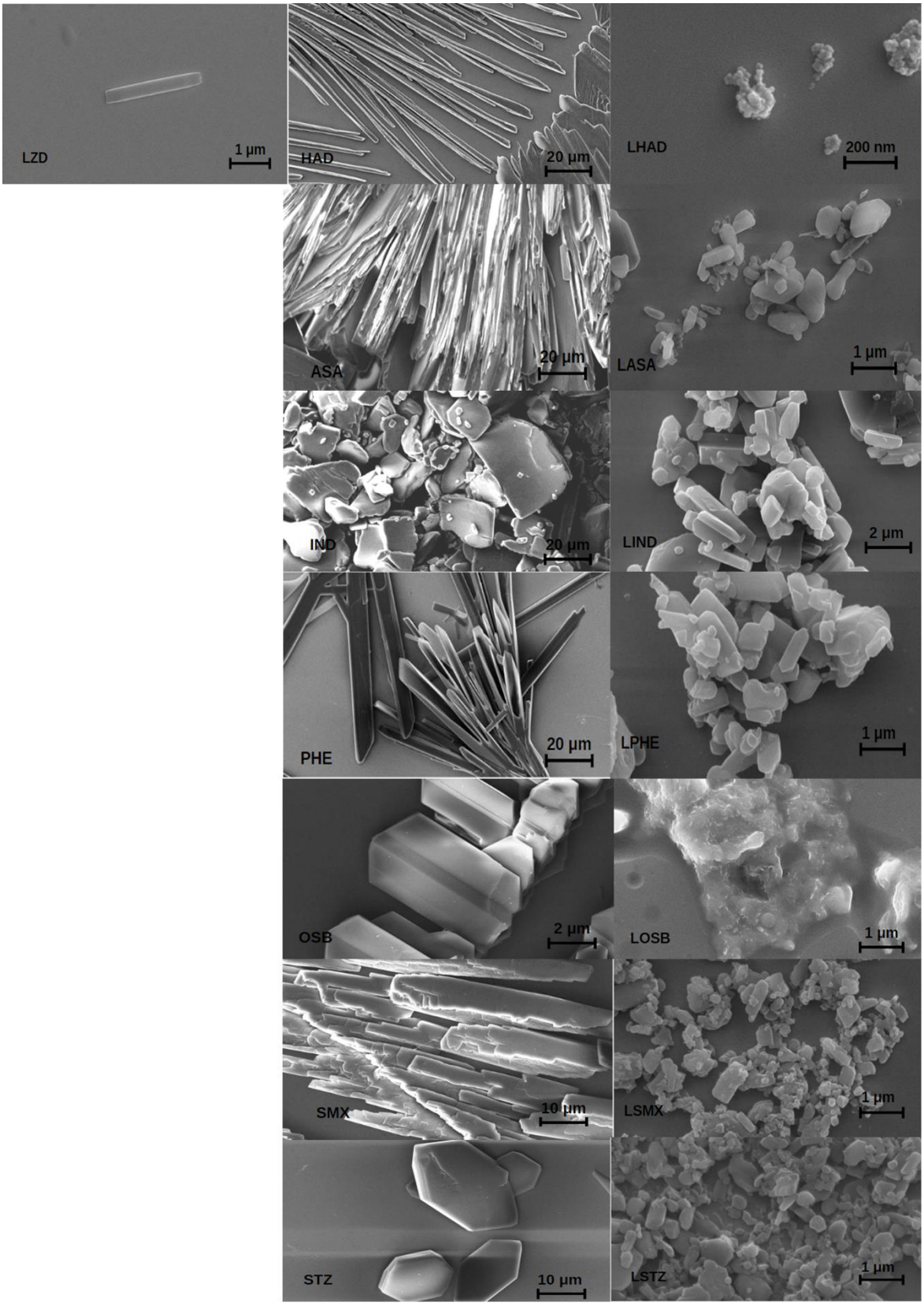


Fig. S6 SEM micrographs of LZD and drug-drug eutectic mixtures.

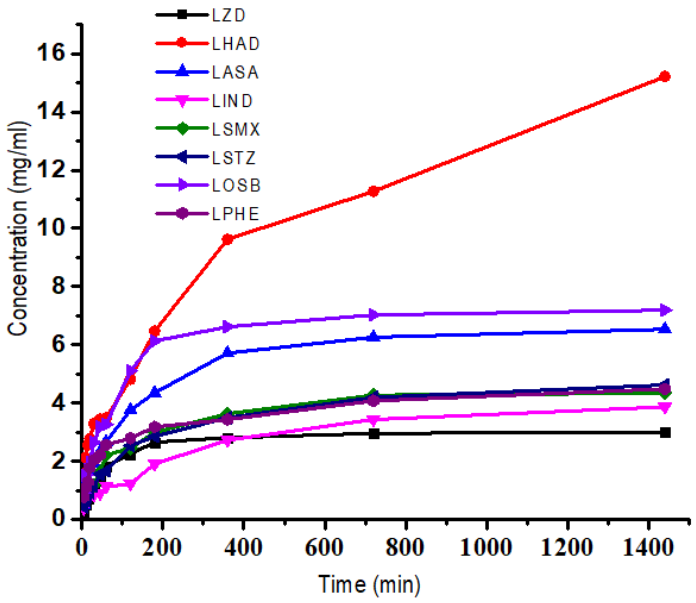


Fig. S7 The experimentally determined solubility curve for 24 hours (1440 minutes).

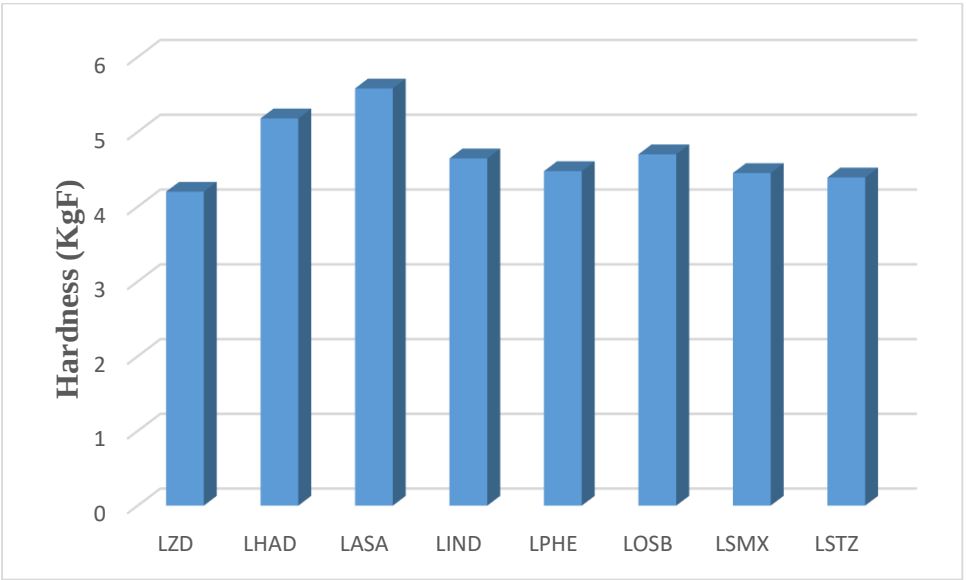


Fig. S8 Hardness of the tablet of the eutectic composites. The tablets were prepared at 75 kg/cm^2 of pressure. (The eutectic mixtures for the tablet preparation were made by mechanochemical milling).

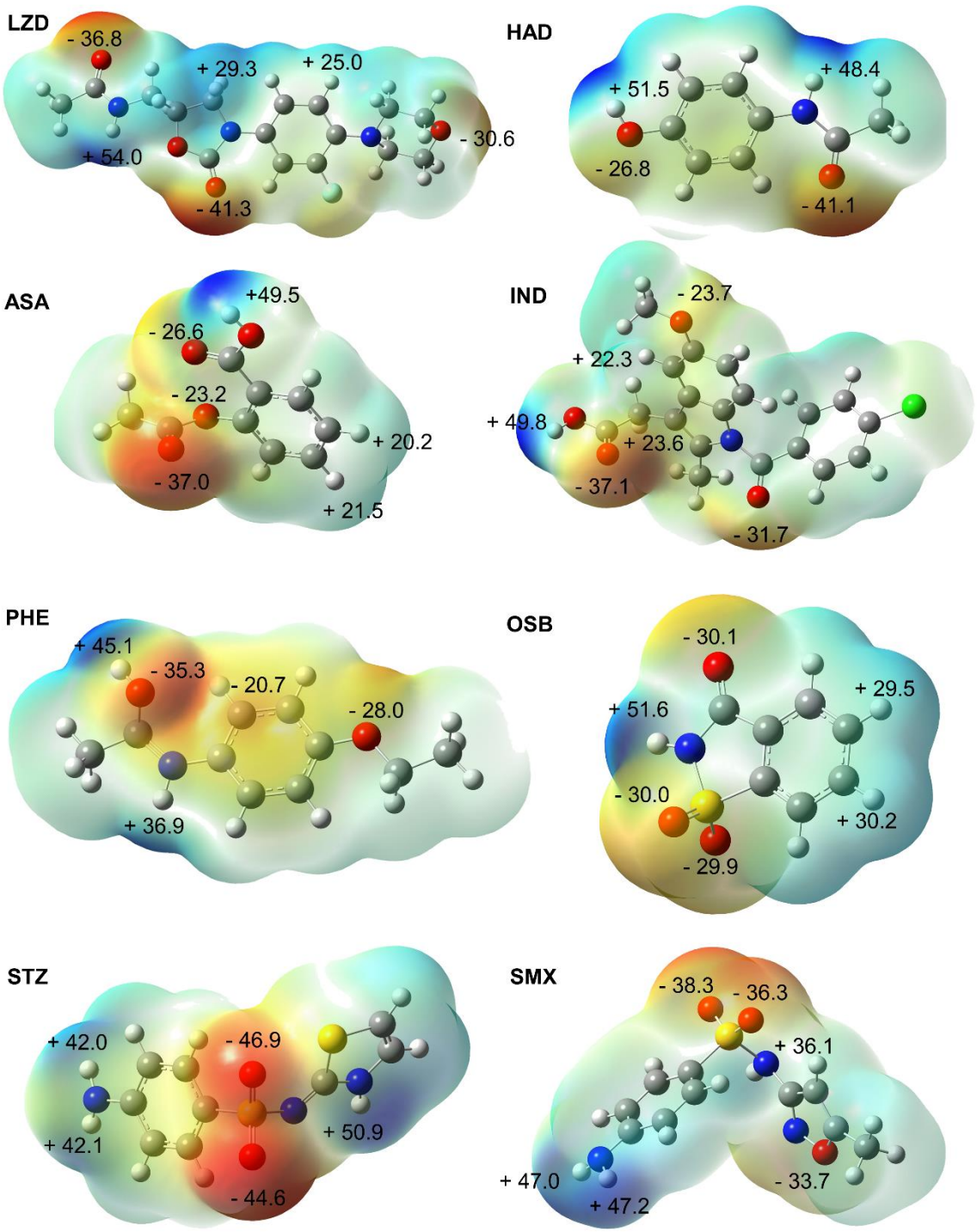


Fig. S9 MESP surfaces of the LZD and Coformer Drugs at the B3LYP/6-311 + G(d,p)/DGDZVP level of theory. The MESP maximum and minimum energies are indicated in kcal mol^{-1}.

Table S1 CCDC Search result using Conquest Software revised on NOV 2022

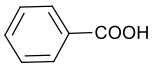
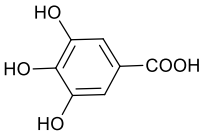
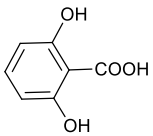
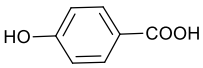
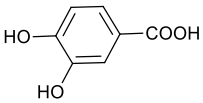
Coformer Structure	Name	CCDC Nos.	Cocrystal Formula
	Benzoic Acid	1993998	C_{16} H_{20} F N_3 O_4, C_7 H_6 O_2
	3,4,5-trihydroxybenzoic acid	1993999	C_{16} H_{20} F N_3 O_4, C_7 H_6 O_5, H_2 O
	2,6-dihydroxybenzoic acid	1994001	C_{16} H_{20} F N_3 O_4, C_7 H_6 O_4
	4-hydroxybenzoic acid	1997194	C_{16} H_{20} F N_3 O_4, C_7 H_6 O_3, H_2 O
	3,4- dihydroxybenzoic acid	1994000	C_{16} H_{20} F N_3 O4, $C_7H_6O_4$, H_2O

Table S2 Melting Temperature multicomponent system.

	T_m (API) (°C)	T_m (mixture) (°C)	Remarks	Composition (mol % of LZD)
LZD (Form-II)	180			
LHAD	169	128	Eutectic	50
LASP	142	106	Eutectic	33
LIND	162	127	Eutectic	60
LPHE	135	120	Eutectic	30
LOSB	220	133	Eutectic	50
LSMX	170	121	Eutectic	50
LSTZ	200	138	Eutectic	33
LIBP	70	75, 143	Physical mixture	—
LSCP	204	155, 204	Physical mixture	—
LSPY	200	154, 200	Physical mixture	—
LSDX	218	155, 218	Physical mixture	—
LSDZ	214	180, 214	Physical mixture	—

T_m: melting temperature

Table S3 The aqueous solubility calculated from the measured absorbance, determined solubility, and standard deviation is given below

LZD

SL NO	TIME	ABS.	CONC. (mg/ml)
1	5 min	0.020	0.237
2	10	0.044	0.518
3	15	0.059	0.693
4	20	0.073	0.855
5	30	0.088	1.030
6	45	0.114	1.335
7	60	0.156	1.824
8	120	0.192	2.242
9	180	0.228	2.652
10	360	0.241	2.805
11	600	0.254	2.954
12	1440	0.258	3.002

TIME	EXP 1	EXP 2	STDEV
5 min	0.020	0.031	0.0074
10	0.044	0.056	0.0085
15	0.059	0.077	0.0123
20	0.073	0.096	0.0161
30	0.088	0.112	0.0171
45	0.114	0.146	0.0222
60	0.156	0.157	0.0007
120	0.192	0.196	0.0023
180	0.228	0.222	0.0041
360	0.241	0.251	0.0072
600	0.254	0.260	0.0045
1440	0.258	0.265	0.0053

LHAD

SL NO	TIME	ABS.	CONC. (mg/ml)
1	5 min	0.129	1.506
2	10	0.182	2.122
3	15	0.219	2.556
4	20	0.239	2.779
5	30	0.283	3.291
6	45	0.296	3.449
7	60	0.3	3.489
8	120	0.414	4.814
9	180	0.556	6.472
10	360	0.827	9.623
11	600	0.969	11.269
12	1440	1.308	15.212

TIME	EXP 1	EXP 2	STDEV
5 min	0.129	0.125	0.0028
10	0.182	0.188	0.0039
15	0.219	0.239	0.0135
20	0.239	0.258	0.0140
30	0.283	0.318	0.0248
45	0.296	0.325	0.0200
60	0.3	0.347	0.0335
120	0.414	0.584	0.1205
180	0.556	0.618	0.0438
360	0.827	0.873	0.0321
600	0.969	0.918	0.0360
1440	1.308	1.192	0.0820

LASA

SL NO	TIME	ABS.	CONC. (mg/ml)
1	5 min	0.043	0.501
2	10	0.115	1.347
3	15	0.114	1.325
4	20	0.146	1.697
5	30	0.165	1.918
6	45	0.199	2.320
7	60	0.229	2.663
8	120	0.322	3.750
9	180	0.373	4.343
10	360	0.491	5.710
11	600	0.538	6.257
12	1440	0.561	6.530

TIME	EXP 1	EXP 2	STDEV
5 min	0.043	0.076	0.0236
10	0.115	0.116	0.0004
15	0.114	0.159	0.0321
20	0.146	0.173	0.0190
30	0.165	0.231	0.0470
45	0.199	0.262	0.0441
60	0.229	0.303	0.0523
120	0.322	0.379	0.0403
180	0.373	0.432	0.0413
360	0.491	0.473	0.0123
600	0.538	0.496	0.0293
1440	0.561	0.532	0.0208

LIND

SL NO	TIME	ABS.	CONC. (mg/ml)
1	5 min	0.033	0.383
2	10	0.057	0.662
3	15	0.062	0.721
4	20	0.066	0.767
5	30	0.074	0.860
6	45	0.078	0.907
7	60	0.096	1.116
8	120	0.105	1.221
9	180	0.164	1.907
10	360	0.234	2.721
11	600	0.295	3.430
12	1440	0.332	3.861

TIME	EXP 1	EXP 2	STDEV
5 min	0.033	0.038	0.0035
10	0.057	0.059	0.0014
15	0.062	0.068	0.0042
20	0.066	0.083	0.0120
30	0.074	0.108	0.0240
45	0.078	0.103	0.0176
60	0.096	0.134	0.0268
120	0.105	0.194	0.0629
180	0.164	0.212	0.0339
360	0.234	0.266	0.0226
600	0.295	0.292	0.0021
1440	0.332	0.3	0.0226

LPHE

SL NO	TIME	ABS.	CONC. (mg/ml)
1	5 min	0.066	0.767
2	10	0.094	1.093
3	15	0.11	1.279
4	20	0.153	1.779
5	30	0.176	2.046
6	45	0.19	2.209
7	60	0.22	2.558
8	120	0.24	2.791
9	180	0.273	3.175
10	360	0.295	3.430
11	600	0.35	4.070
12	1440	0.385	4.477

TIME	EXP 1	EXP 2	STDEV
5 min	0.066	0.078	0.0084
10	0.094	0.95	0.6052
15	0.11	0.12	0.0070
20	0.153	0.14	0.0091
30	0.176	0.187	0.0077
45	0.19	0.2	0.0070
60	0.22	0.21	0.0070
120	0.24	0.238	0.0014
180	0.273	0.28	0.0049
360	0.295	0.3	0.0035
600	0.35	0.34	0.0070
1440	0.385	0.38	0.0035

LOSB

SL NO	TIME	ABS.	CONC. (mg/ml)
1	5 min	0.078	0.907
2	10	0.13	1.511
3	15	0.147	1.709
4	20	0.168	1.953
5	30	0.228	2.651
6	45	0.273	3.175
7	60	0.28	3.256
8	120	0.439	5.105
9	180	0.527	6.129
10	360	0.569	6.617
11	600	0.604	7.024
12	1440	0.618	7.187

TIME	EXP 1	EXP 2	STDEV
5 min	0.078	0.069	0.0063
10	0.13	0.124	0.0042
15	0.147	0.156	0.0063
20	0.168	0.174	0.0042
30	0.228	0.236	0.0056
45	0.273	0.265	0.0056
60	0.28	0.282	0.0014
120	0.439	0.424	0.0106
180	0.527	0.464	0.0445
360	0.569	0.548	0.0148
600	0.604	0.551	0.0374
1440	0.618	0.598	0.0141

LSMX

SL NO	TIME	ABS.	CONC. (mg/ml)
1	5 min	0.063	0.732
2	10	0.07	0.814
3	15	0.084	0.976
4	20	0.088	1.023
5	30	0.101	1.174
6	45	0.14	1.628
7	60	0.19	2.209
8	120	0.21	2.442
9	180	0.257	2.988
10	360	0.312	3.628
11	600	0.367	4.268
12	1440	0.373	4.338

TIME	EXP 1	EXP 2	STDEV
5 min	0.063	0.055	0.0056
10	0.07	0.08	0.0070
15	0.084	0.09	0.0042
20	0.088	0.101	0.0091
30	0.101	0.12	0.0134
45	0.14	0.134	0.0042
60	0.19	0.184	0.0042
120	0.21	0.235	0.0176
180	0.257	0.249	0.0056
360	0.312	0.31	0.0014
600	0.367	0.34	0.0190
1440	0.373	0.356	0.0120

LSTZ

SL NO	TIME	ABS.	CONC. (mg/ml)
1	5 min	0.037	0.430
2	10	0.055	0.639
3	15	0.069	0.802
4	20	0.08	0.930
5	30	0.098	1.139
6	45	0.133	1.546
7	60	0.143	1.663
8	120	0.218	2.535
9	180	0.245	2.849
10	360	0.3	3.489
11	600	0.36	4.186
12	1440	0.397	4.617

TIME	EXP 1	EXP 2	STDEV
5 min	0.037	0.049	0.0084
10	0.055	0.061	0.0042
15	0.069	0.079	0.0070
20	0.08	0.082	0.0014
30	0.098	0.097	0.0007
45	0.133	0.14	0.0049
60	0.143	0.154	0.0077
120	0.218	0.22	0.0014
180	0.245	0.263	0.0127
360	0.3	0.31	0.0070
600	0.36	0.35	0.0070
1440	0.397	0.41	0.0091

Table S4 The % availability of LZD in drug-drug eutectic mixture

	% Amount of LZ		STD DEV
LZD	96.26	97.16	0.632
LHAD	93.46	92.81	0.462
LASA	88.83	90.02	0.844
LPHE	74.60	74.70	0.072
LOSB	93.46	93.75	0.207
LSMX	76.80	75.51	0.909
LSTZ	88.94	88.05	0.628

Table S5 The % availability of coformer drug in drug-drug eutectic mixture

	% Availability of coformer drug in drug-drug eutectic mixture		STD DEV	EXPECTED AS PER USP	EXPECTED AS PER IP
LHAD	90.12	91.51	0.982	> 80% 30 MIN	> 80% 30 MIN
LASA	85.74	85.73	0.009	>80% 30 MIN	>70% 45 MIN
LPHE	74.10	74.53	0.299	NA	NA
LOSB	94.16	95.09	0.654	NA	NA
LSMX	77.96	77.60	0.256	> 70% 60 MIN	NA
LSTZ	87.53	86.44	0.767	NA	NA