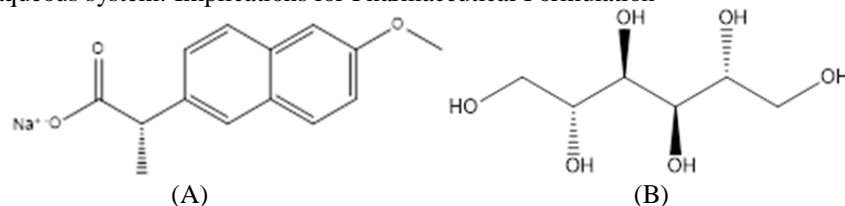


## Supplementary data

Thermo-acoustic and computational studies for intermolecular interactions in a mixture of drug (NSAIDs) and D-mannitol in an aqueous system: Implications for Pharmaceutical Formulation



**Fig. S1:** Chemical structure of (A) sodium naproxen and (B) D-mannitol

**Table S1:** Comparison of density ( $\rho$ ) and sound velocity ( $u$ ) of water with reported values.

Temperature(K)	Density ( $\rho$ ), (g/cm <sup>3</sup> )		Sound velocity( $u$ ), (m/s)	
	Experimental	Literature	Experimental	Literature
293.15	0.998226	0.998202 <sup>d</sup> 0.998226 <sup>e</sup>	1483.10	1483.10 <sup>f</sup> 1482.55 <sup>b</sup>
298.15	0.997100	0.997100 <sup>g</sup> 0.997046 <sup>h</sup>	1497.00	1497.00 <sup>d</sup> 1497.65 <sup>l</sup>
303.15	0.995238	0.995241 <sup>i</sup> 0.995651 <sup>j</sup>	1509.34	1509.57 <sup>k</sup> 1509.10 <sup>c</sup>
308.15	0.994030	0.994037 <sup>e</sup> 0.994058 <sup>d</sup>	1519.34	1520.17 <sup>a</sup> 1519.83 <sup>d</sup>
313.15	0.992212	0.992210 <sup>d</sup> 0.992214 <sup>b</sup>	1529.30	1529.89 <sup>a</sup> 1529.35 <sup>b</sup>

The standard uncertainties in density ( $\rho$ ), sound velocity ( $u$ ), temperature ( $T$ ), and pressure ( $P$ ) are  $\pm 1 \times 10^{-6}$  g cm<sup>-3</sup>,  $\pm 0.029$  m/s<sup>1</sup>,  $\pm 10^{-2}$  K and  $\pm 5$  kPa respectively.

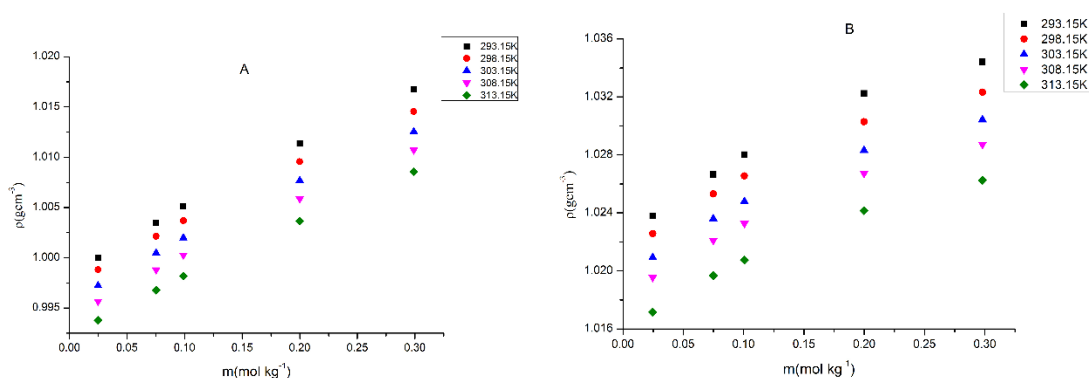
<sup>a</sup> (Shahazidy *et al.*, 2022), <sup>b</sup> (Jamal *et al.*, 2021), <sup>c</sup> (Jamal *et al.*, 2017), <sup>d</sup> (Naseem *et al.*, 2016), <sup>e</sup> (Sajid *et al.*, 2021), <sup>f</sup> (Jamal *et al.*, 2022), <sup>g</sup> (Warmańska, 2012), <sup>h</sup> (Kumar *et al.*, 2021), <sup>i</sup> (Jiang *et al.*, 2013), <sup>j</sup> (Li *et al.*, 2013), <sup>k</sup> (Naseem *et al.*, 2017), <sup>l</sup> (Shahazidy *et al.*, 2024)

**Table S2:** Experimental densities ( $\rho$ ) of sodium naproxen (Na-NAP) in water and different concentrations of D-mannitol (% w/w) at T= (293.15K-313.15K) and atmospheric pressure.

Concentration of sodium naproxen m/mol kg <sup>-1</sup>	Density( $\rho$ ), (g/cm <sup>3</sup> )				
	293.15 K	298.15 K	303.15 K	308.15 K	313.15 K
Sodium Naproxen + water					
0.0000	0.998226	0.997100	0.995238	0.994030	0.992212
0.0247	1.000010	0.998820	0.997228	0.995645	0.993766
0.0748	1.003487	1.002137	1.000465	0.998751	0.996742
0.1006	1.005127	1.003697	1.001975	1.000202	0.998132
0.1998	1.011342	1.009553	1.007688	1.005801	1.003507
0.2979	1.016783	1.014549	1.012540	1.010661	1.008198
Sodium Naproxen in 5% aqueous D-mannitol					
0.0000	1.013209	1.012254	1.011351	1.008632	1.008426
0.0247	1.023781	1.022582	1.020928	1.019554	1.017155
0.0748	1.026660	1.025317	1.023603	1.022113	1.019667
0.1006	1.028045	1.026596	1.024788	1.023277	1.020757
0.1998	1.032093	1.030368	1.028315	1.026722	1.024155
0.2979	1.03472	1.032333	1.030458	1.028725	1.026254
Sodium Naproxen in 7% aqueous D-mannitol					
0.0000	1.023314	1.021462	1.020375	1.018477	1.016147
0.0247	1.030882	1.029758	1.028625	1.026677	1.025303
0.0748	1.033321	1.031979	1.030645	1.028755	1.027317
0.1006	1.034203	1.032804	1.031387	1.029531	1.028101

0.1998	1.037472	1.035901	1.034059	1.032311	1.030743
0.2979	1.039132	1.037542	1.035604	1.033802	1.032212
Sodium Naproxen in 9% w/w aqueous D-mannitol					
0.0000	1.027482	1.026624	1.024764	1.022587	1.020454
0.0247	1.041557	1.039624	1.037538	1.035617	1.033232
0.0748	1.043302	1.041225	1.039046	1.037031	1.034542
0.1006	1.043834	1.041754	1.039538	1.037466	1.03492
0.1998	1.046003	1.043801	1.041463	1.039049	1.036349
0.2979	1.047804	1.045379	1.043019	1.04027	1.037598
Sodium Naproxen in 10% aqueous D-mannitol					
0.0000	1.030325	1.028768	1.026785	1.024876	1.021843
0.0247	1.046385	1.044570	1.043198	1.039942	1.038217
0.0748	1.047976	1.046021	1.04456	1.041214	1.039337
0.1006	1.048491	1.046453	1.044906	1.041529	1.039576
0.1998	1.050387	1.048085	1.046171	1.042526	1.040176
0.2979	1.052005	1.049018	1.046886	1.043086	1.040189

Density ( $\rho$ ), temperature ( $T$ ), and pressure ( $P$ ) all have standard errors of  $\pm 1 \times 10^{-3}$  g/cm<sup>3</sup>,  $\pm 10^{-2}$  K, and  $\pm 5$  kPa, respectively

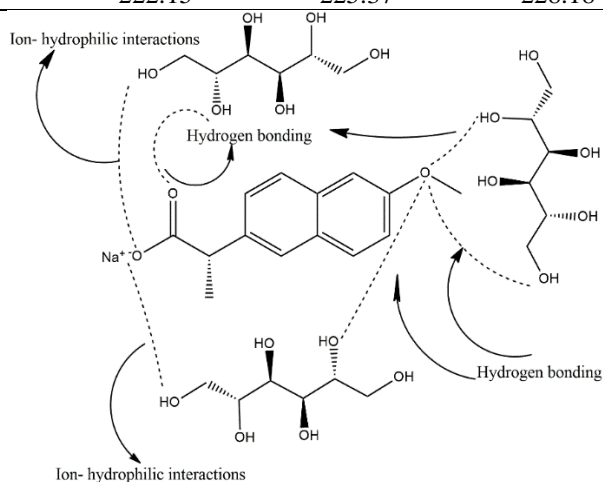


**Fig. S2:** Plots of density ( $\rho$ ) and molality ( $m$ ) of Na-NAP in water, (A) 5% D-mannitol and (B) 7% D-mannitol

**Table S3:** Molality ( $m$ ) and Apparent molar volume ( $\phi_v$ ) of sodium naproxen (Na-NAP) in water and different concentrations of aqueous D-mannitol (%w/w) at  $T = (293.15\text{K}-313.15\text{K})$  and atmospheric pressure

Concentration of sodium naproxen $m/\text{mol kg}^{-1}$	Apparent molar volume ( $\phi_v$ ), (cm <sup>3</sup> /mol)				
	293.15 K	298.15 K	303.15 K	308.15 K	313.15 K
Sodium Naproxen + water					
0.0247	180.69	183.40	185.20	187.89	190.651
0.0748	181.65	184.79	186.59	189.39	192.25
0.1006	182.11	185.34	187.26	190.03	192.87
0.1998	184.78	188.31	190.12	192.20	194.92
0.2979	187.09	191.09	192.89	194.35	196.88
Sodium Naproxen in 5% w/w aqueous D-mannitol					
0.0247	185.59	187.45	189.66	191.62	193.51
0.0748	189.05	191.63	193.29	195.57	197.05
0.1006	190.23	193.20	195.40	197.37	199.29
0.1998	197.53	200.53	203.00	204.53	205.95
0.2979	204.09	208.44	209.63	211.23	212.02
Sodium Naproxen in 7% w/w aqueous D-mannitol					
0.0247	192.58	195.53	197.67	199.67	201.55
0.0748	196.15	200.03	203.36	203.56	205.17
0.1006	198.26	201.88	205.33	205.23	206.44
0.1998	205.72	208.44	212.33	212.33	213.34
0.2979	210.12	212.24	215.51	215.51	216.69
Sodium Naproxen in 9% w/w aqueous D-mannitol					

0.0247	201.75	203.71	206.00	208.69	210.95
0.0748	206.19	208.91	211.12	213.47	215.48
0.1006	207.66	209.95	212.19	214.75	217.37
0.1998	213.03	215.03	217.02	220.34	222.44
0.2979	216.19	218.45	220.00	223.56	225.24
Sodium Naproxen in 10% w/w aqueous D-mannitol					
0.0247	202.65	205.16	207.71	210.27	213.26
0.0748	207.65	210.50	212.67	215.10	218.30
0.1006	208.77	212.00	214.69	217.10	220.54
0.1998	214.47	217.70	221.16	224.16	228.25
0.2979	217.42	222.15	225.37	228.18	233.04



**Fig. S3:** Different possible interactions between Na-NAP and D-mannitol

**Table S4:** Sound velocity ( $u$ ) for sodium naproxen (Na-NAP) in water and different concentrations of D-mannitol (% w/w) at T= (293.15K-313.15K) and atmospheric pressure.

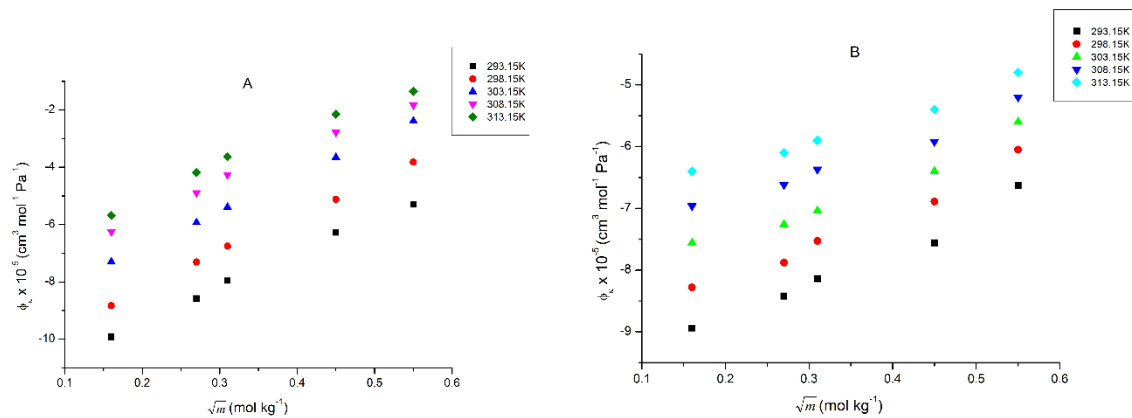
Concentration of sodium naproxen $m/mol\ g^{-1}$	Sound velocity ( $u$ ), ( $m/s^1$ )				
	293.15 K	298.15 K	303.15 K	308.15 K	313.15 K
Sodium Naproxen + water					
0.0000	1483.10	1497.00	1509.34	1519.34	1529.30
0.0247	1489.16	1502.82	1514.64	1524.36	1534.22
0.0748	1499.94	1512.87	1523.83	1532.89	1542.35
0.1006	1504.55	1517.24	1527.76	1536.35	1545.73
0.1998	1521.74	1533.26	1541.34	1549.07	1557.71
0.2979	1537.02	1545.74	1551.66	1559.61	1568.15
Sodium Naproxen in 5% w/w aqueous D-mannitol					
0.0000	1517.43	1529.22	1541.79	1549.14	1557.60
0.0247	1523.87	1535.52	1547.93	1555.11	1563.39
0.0748	1536.76	1548.33	1560.49	1567.28	1575.25
0.1006	1543.15	1554.58	1566.90	1573.39	1581.43
0.1998	1569.09	1579.88	1591.92	1598.11	1605.19
0.2979	1592.67	1604.04	1615.25	1621.32	1628.05
Sodium Naproxen in 7% w/w aqueous D-mannitol					
0.0000	1530.73	1542.78	1544.32	1561.45	1569.76
0.0247	1537.56	1549.55	1561.10	1568.09	1576.35
0.0748	1550.19	1561.97	1573.56	1580.22	1588.42
0.1006	1555.25	1566.91	1578.23	1584.84	1592.87
0.1998	1577.41	1588.01	1599.15	1605.78	1613.18
0.2979	1591.98	1601.97	1611.42	1617.49	1624.62
Sodium Naproxen in 9% w/w aqueous D-mannitol					
0.0000	1543.12	1555.56	1566.03	1573.12	1583.13

0.0247	1550.45	1562.67	1573.09	1580.09	1590.07
0.0748	1563.83	1575.85	1586.06	1592.72	1602.56
0.1006	1568.53	1580.44	1590.28	1596.94	1606.62
0.1998	1591.57	1602.7	1612.35	1618.04	1627.14
0.2979	1611.41	1622.43	1631.86	1637.72	1646.52
Sodium Naproxen in 10% w/w aqueous D-mannitol					
0.0000	1550.51	1562.34	1573.56	1582.45	1589.23
0.0247	1557.82	1569.62	1580.76	1589.51	1596.25
0.0748	1571.28	1583.09	1593.94	1602.46	1609.26
0.1006	1575.67	1587.43	1598.53	1606.88	1613.75
0.1998	1597.84	1608.93	1620.11	1628.21	1635.36
0.2979	1618.35	1629.82	1638.86	1646.71	1654.34

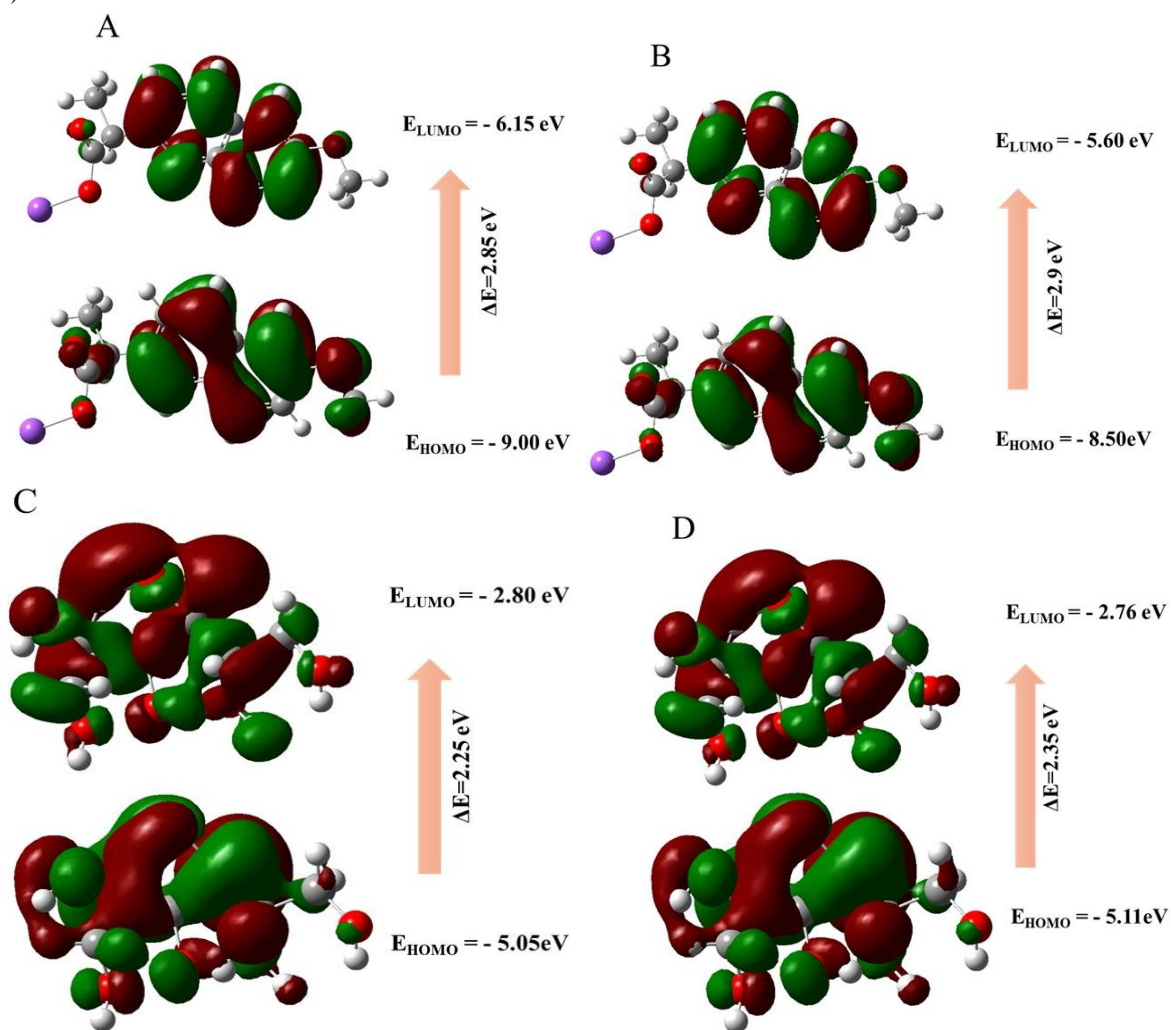
Speed of sound ( $u$ ), ( $\rho$ , temperature ( $T$ ), and pressure ( $P$ ) all have standard errors of  $\pm 0.029 \text{ m/s}^1$ ,  $\pm 10^{-2} \text{ K}$ , and  $\pm 5 \text{ kPa}$ , respectively.

**Table S5:** Molality ( $m$ ) and Apparent molar isentropic compressibility ( $\phi_k$ ) of sodium naproxen (Na-NAP) in water and different concentrations of aqueous D-mannitol (%w/w) at  $T = (293.15\text{K}-313.15\text{K})$  and atmospheric pressure.

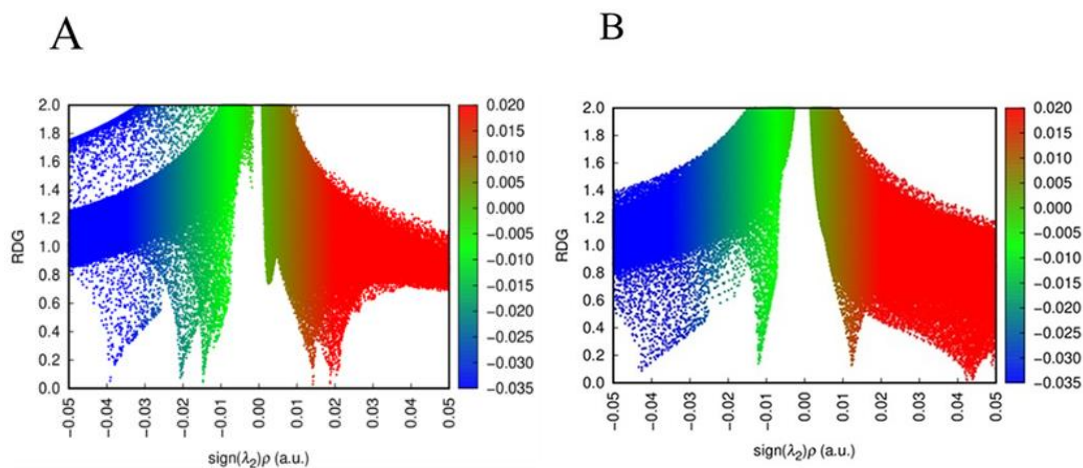
Concentration of sodium naproxen $m/\text{mol kg}^{-1}$	Apparent molar isentropic compressibility ( $\phi_k \times 10^{-5}$ ), ( $\text{cm}^3/\text{mol Pa}$ )				
	293.15 K	298.15 K	303.15 K	308.15 K	313.15 K
Sodium Naproxen +water					
0.0247	-9.92	-8.83	-7.3	-6.25	-5.68
0.0748	-8.58	-7.31	-5.93	-5.09	-4.18
0.1006	-7.95	-6.75	-5.39	-4.26	-3.63
0.1998	-6.28	-5.12	-3.65	-2.78	-2.15
0.2979	-5.29	-3.82	-2.38	-1.83	-1.35
Sodium Naproxen in 5% w/w aqueous D-mannitol					
0.0247	-8.94	-8.28	-7.56	-6.96	-6.4
0.0748	-8.42	-7.88	-7.26	-6.62	-6.10
0.1006	-8.14	-7.53	-7.04	-6.37	-5.90
0.1998	-7.56	-6.89	-6.40	-5.92	-5.40
0.2979	-6.63	-6.05	-5.60	-5.20	-4.80
Sodium Naproxen in 7% w/w aqueous D-mannitol					
0.0247	-8.61	-8.08	-7.76	-7.29	-6.87
0.0748	-7.48	-6.82	-6.52	-6.04	-5.75
0.1006	-6.95	-6.29	-5.87	-5.44	-5.13
0.1998	-5.29	-4.57	-4.24	-3.93	-3.54
0.2979	-4.30	-3.65	-3.08	-2.76	-2.39
Sodium Naproxen in 9% w/w aqueous D-mannitol					
0.0247	-8.11	-7.34	-6.93	-6.49	-6.14
0.0748	-7.16	-6.51	-6.06	-5.54	-5.17
0.1006	-6.85	-6.25	-5.64	-5.17	-4.72
0.1998	-5.85	-5.22	-4.77	-4.12	-3.65
0.2979	-4.68	-4.16	-3.79	-3.30	-2.92
Sodium Naproxen in 10% w/w aqueous D-mannitol					
0.0247	-7.89	-7.46	-6.95	-6.43	-6.07
0.0748	-6.99	-6.61	-6.06	-5.59	-5.31
0.1006	-6.55	-6.12	-5.72	-5.22	-4.95
0.1998	-5.38	-4.82	-4.44	-3.99	-3.74
0.2979	-4.37	-3.94	-3.26	-2.86	-2.62



**Fig. S4:** Plots of Apparent molar isentropic compressibility ( $\phi_k$ ) and molality ( $m$ ) of (A) Na-NAP in water and (B) 5% D-mannitol



**Fig. S5:** HOMO-LUMO representation of (A) Na-NAP<sub>(gas)</sub>, (B) Na-NAP<sub>(aqueous)</sub>, (C) D-mannitol<sub>(gas)</sub> and (D) D-mannitol<sub>(aqueous)</sub>



**Fig. S6:** RDG vs  $\text{sign}(\lambda_2)\rho$  plot of (A) Na-NAP and (B) D-mannitol

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