

Supplementary data for the article:

Marković, O. S.; Pešić, M. P.; Shah, A. V.; Serajuddin, A. T. M.; Verbić, T. Ž.; Avdeef, A. Solubility-PH Profile of Desipramine Hydrochloride in Saline Phosphate Buffer: Enhanced Solubility Due to Drug-Buffer Aggregates. *European Journal of Pharmaceutical Sciences* **2019**, *133*, 264–274. <https://doi.org/10.1016/j.ejps.2019.03.014>

Supplementary material

Solubility-pH profile of desipramine hydrochloride in saline phosphate buffer: enhanced solubility due to drug-buffer aggregates

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Tables S4-S10 summarize the 25°C titration data (titrant volumes and pH_{final}) of desipramine hydrochloride (or free base) in a procedure guided by *pDISOL-X* simulations (pH-Ramp Shake-Flask method) and consensus recommendations of a recent “white paper” on solubility methodology (Avdeef *et al.* 2016). The final pH measurements were obtained after equilibration (6 h stir, followed by 18 h sedimentation without stirring). All drug concentrations were measured by HPLC-UV/VIS.

Table S1. Initial composition of stock suspensions

Set	V_{init} (ml)	m_{DsHCl} (g) ^a	pH_{init}	[DsHCl] ^c (M)	[NaH ₂ PO ₄] ^c (M)	[Cl] _{tot} (M) ^c
1	50.0 ^b	0.41170	11.62	0.03	0.12	0.03
2	50.0 ^b	0.41220	11.61	0.03	0.12	0.03
3	15.0 ^b	0.34370	1.90	0.08	0.14	0.14
4	0.900 ^c	0.08650-0.08730	4.34	0.32	0.15	0.32
5	1.000 ^d	0.04745-0.11205	1.31-10.04	0.15-0.37	–	0.15-0.40

^aWeight of DsHCl added to the initial volumes indicated.

^bInitial volume of stock suspension which was further apportioned into 1 or 2 mL aliquots and pH-adjusted with HCl/NaOH (*cf.*, **Tables S4-S6**).

^cInitial volume of 0.15 M NaH₂PO₄, the pH of which was adjusted with H₃PO₄, or HCl, or NaOH (*cf.*, **Table S7**).

^dInitial volume of 0.15 M NaCl, the pH of which was adjusted with HCl or NaOH (*cf.*, **Table S8**).

^eTotal quantity of DsHCl/NaH₂PO₄/Cl per 1 L of initial prepared suspension.

Table S2. Series 1 – concentrated suspension to collect compound for solid state characterisation^a

Sample	$V_{\text{NaH}_2\text{PO}_4}$ (ml)	m_{DsHCl} (g) ^b	pH_{init}	V_{HCl} (μl)	V_{NaOH} (μl)	pH_{final}	[DsHCl] (M) ^c	[NaH ₂ PO ₄] (M) ^c	[Cl] _{tot} (M) ^c
OM11	2.000	0.17615	3.92	100	–	2.09	0.28	0.14	0.33
OM12	2.000	0.16315	3.90	–	20	3.86	0.27	0.15	0.27
OM13	2.000	0.15035	3.78	–	270	7.41	0.22	0.13	0.22
OM14	2.000	0.13580	3.80	–	300	9.57	0.19	0.13	0.19
OM15	2.000	0.13950	3.84	–	600	11.10	0.18	0.12	0.18

^a2-mL solutions of 0.15 M NaH₂PO₄ with pH adjusted by HCl/NaOH: titrants $c_{\text{HCl}}=1.0211$ M and $c_{\text{NaOH}}=1.1047$ M. See text.

^bWeight of DsHCl added to 2-mL volumes of 0.15 M NaH₂PO₄.

^cTotal quantity of DsHCl/NaH₂PO₄/Cl per 1 L of final suspension.

Table S3. Series 2 – concentrated suspension to collect compound for solid state characterization

Sample	$V_{\text{NaH}_2\text{PO}_4}$ (ml)	$m_{\text{NaH}_2\text{PO}_4 \cdot 2\text{H}_2\text{O}}$ (g)	$V_{\text{H}_2\text{O}}$ (ml)	m_{Ds} (g)	m_{DsHCl} (g)	pH_{init}	$V_{\text{H}_3\text{PO}_4}$ (μl)	V_{NaOH} (μl)	pH_{final}	[Ds] _{tot} (M) ^c	[PO ₄] _{tot} (M) ^c	[Cl] _{tot} (M) ^c
OM21 ^a	0.90 ^b	–	–	0.09605	–	5.99	400	–	2.13	0.28	0.31	–
OM22	2.00 ^b	–	–	–	0.14995	3.87	–	–	3.84	0.25	0.15	0.25
OM23	–	0.07000	3.000	–	0.24980	3.95	–	410	8.03	0.24	0.13	0.24
OM24	–	0.06995	3.000	–	0.24985	3.96	–	450	9.44	0.24	0.13	0.24
OM25	–	0.04945	2.000	–	0.12455	4.00	–	680	11.10	0.15	0.12	0.15

^aChloride-free.

^bInitial volumes of 0.15 M NaH₂PO₄, with pH adjusted by H₃PO₄/NaOH: titrants $c_{\text{H}_3\text{PO}_4}=1.0048$ M and $c_{\text{NaOH}}=1.1047$ M. See text.

^cTotal quantity of DsHCl/NaH₂PO₄/Cl per 1 L of final suspension.

Table S4. Set 1 – desipramine hydrochloride high-to-low pH titration and solubility data^a

Sample	pH _{init}	V _{HCl} (μL)	V _{NaOH} (μL)	pH _{final}	S (M)	log S
1	11.27	410	–	4.42	1.48×10 ⁻²	-1.83
2	11.52	350	–	6.00	2.59×10 ⁻³	-2.59
3	11.60	320	–	6.51	1.86×10 ⁻³	-2.73
4	11.55	205	–	7.39	1.29×10 ⁻³	-2.89
5	11.48	194	5	7.97	1.27×10 ⁻³	-2.90
6	11.33	210	40	8.55	1.22×10 ⁻³	-2.91
7	11.49	180	5	8.72	1.27×10 ⁻³	-2.90
8	11.56	143	–	9.46	1.25×10 ⁻³	-2.90
9	11.50	130	10	9.81	1.11×10 ⁻³	-2.95
10	11.52	130	–	10.10	6.74×10 ⁻⁴	-3.17
11	11.50	100	–	10.62	3.06×10 ⁻⁴	-3.51
12	11.60	50	–	11.26	1.98×10 ⁻⁴	-3.70
13	11.56	–	–	11.55	1.71×10 ⁻⁴	-3.77

^aInitial suspension volume 2 mL. Phases separated by filtration. No solid detected below pH 4.

Titriments added in increments during mixing as pH was changing: c_{HCl} = 0.9896 M, c_{NaOH} = 1.0074 M

Table S5. Set 2 – desipramine hydrochloride high-to-low pH titration and solubility data^a

Sample	pH _{init}	V _{HCl} (μL)	V _{NaOH} (μL)	pH _{final}	S (M)	log S
1	11.51	400	–	4.78	9.71×10 ⁻³	-2.01
2	11.58	401	20	5.36	5.29×10 ⁻³	-2.28
3	11.60	360	–	6.03	2.79×10 ⁻³	-2.55
4	11.59	300	–	6.58	1.87×10 ⁻³	-2.73
5	11.56	200	–	7.50	1.34×10 ⁻³	-2.87
6	11.45	170	–	7.78	1.15×10 ⁻³	-2.94
7	11.62	180	20	8.12	1.13×10 ⁻³	-2.95
8	11.54	163	20	8.47	1.14×10 ⁻³	-2.94
9	11.48	130	–	9.71	1.22×10 ⁻³	-2.91
10	11.61	125	–	10.06	5.81×10 ⁻³	-3.24
11	11.51	100	–	10.56	2.62×10 ⁻³	-3.58
12	11.57	50	–	11.02	1.80×10 ⁻³	-3.74
13	11.55	–	–	11.34	2.66×10 ⁻³	-3.58

^aSee footnotes in **Table S4**.

Table S6. Set 3 – desipramine hydrochloride low-to-high pH titration and solubility data^a

Sample	pH _{init}	V _{NaOH} (μL)	V _{HCl} (μL)	pH _{final}	S (M)	log S
1	1.86	80	–	3.99	4.51×10 ⁻²	-1.35
2	1.87	100	–	4.73	1.13×10 ⁻²	-1.95
3	1.89	150	50	5.19	9.24×10 ⁻³	-2.03
4	1.88	120	–	6.04	3.30×10 ⁻³	-2.48
5	1.88	150	–	6.69	2.23×10 ⁻³	-2.65
6	1.92	180	–	7.14	1.78×10 ⁻³	-2.75
7	1.94	200	–	7.79	1.70×10 ⁻³	-2.77
8	1.91	220	–	9.64	1.69×10 ⁻³	-2.77
9	1.91	280	–	10.08	4.68×10 ⁻⁴	-3.33
10	1.89	325	–	11.00	1.55×10 ⁻⁴	-3.81
11	1.91	370	–	11.47	1.35×10 ⁻⁴	-3.87

^aInitial solution volumes were 1 mL in all cases. Phases separated by centrifugation. Otherwise, see footnote in **Table S4**.

Table S7. Set 4 – concentrated desipramine hydrochloride solubility data^a

Sample	V _{NaH₂PO₄} (mL)	m _{DsHCl} (g)	V _{NaOH} (μL)	V _{H₃PO₄} (μL)	V _{HCl} (μL)	pH _{final}	S (M) ^d	log S
1	0.90	0.08660	–	40	–	2.42	0.281	-0.55
2	0.90	0.08650	10	13	–	3.59	0.288	-0.54
3	0.90	0.08730	–	–	50	2.02	0.245	-0.61

^aStock [NaH₂PO₄] = 0.15 M, pH 4.34. Titrant concentrations: c_{HCl} = 1.0032 M, c_{NaOH} = 1.0215 M, c_{H₃PO₄} = 1.0048 M. Phases separated by centrifugation for Samples 1 and 2, and by filtration for Sample 3.

Table S8. Set 5 – phosphate-free desipramine hydrochloride titration and solubility data^a

Sample	m _{DsHCl} (g)	V _{NaOH} (μL)	V _{HCl} (μL)	pH _{final}	S (M)	log S
1	0.10955	53	100	1.31	2.78×10 ⁻²	-1.56
2	0.11205	–	4	2.38	3.00×10 ⁻²	-1.52
3	0.09140	23	25	3.02	3.88×10 ⁻²	-1.41
4	0.05300	–	–	4.93	4.32×10 ⁻²	-1.36
5	0.04745	5	–	7.59	8.24×10 ⁻²	-1.08
6	0.05475	130	–	8.98	3.79×10 ⁻³	-2.42
7	0.05120	170	–	10.04	5.02×10 ⁻⁴	-3.30

^aInitially, each sample vial contained 1 mL 0.15 M NaCl. Titrant concentrations: c_{HCl} 1.0211 M, c_{NaOH} 1.0215 M.

Table S9. Series 1 – solubility-pH results

Sample	pH _{final}	S (M)	log S
OM11	2.09	0.200	-0.70
OM12	3.86	0.228	-0.64
OM13	7.41	2.65×10^{-3}	-2.58
OM14	9.57	1.80×10^{-3}	-2.75
OM15	11.10	9.37×10^{-5}	-4.03

Table S10. Series 2 – solubility-pH results

Sample	pH _{final}	S (M)	log S
OM21 ^a	2.13	2.87×10^{-2}	-1.54
OM22	3.84	2.37×10^{-1}	-0.63
OM23	8.03	3.34×10^{-3}	-2.48
OM24	9.44	2.66×10^{-3}	-2.57
OM25	11.10	1.50×10^{-4}	-3.82

^aChloride-free.

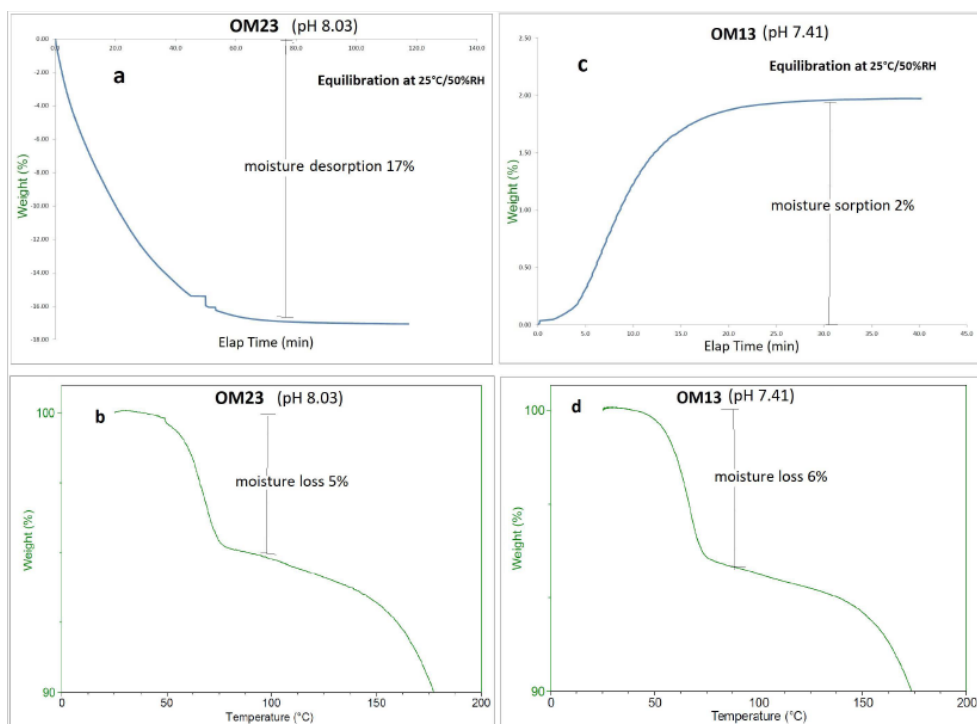
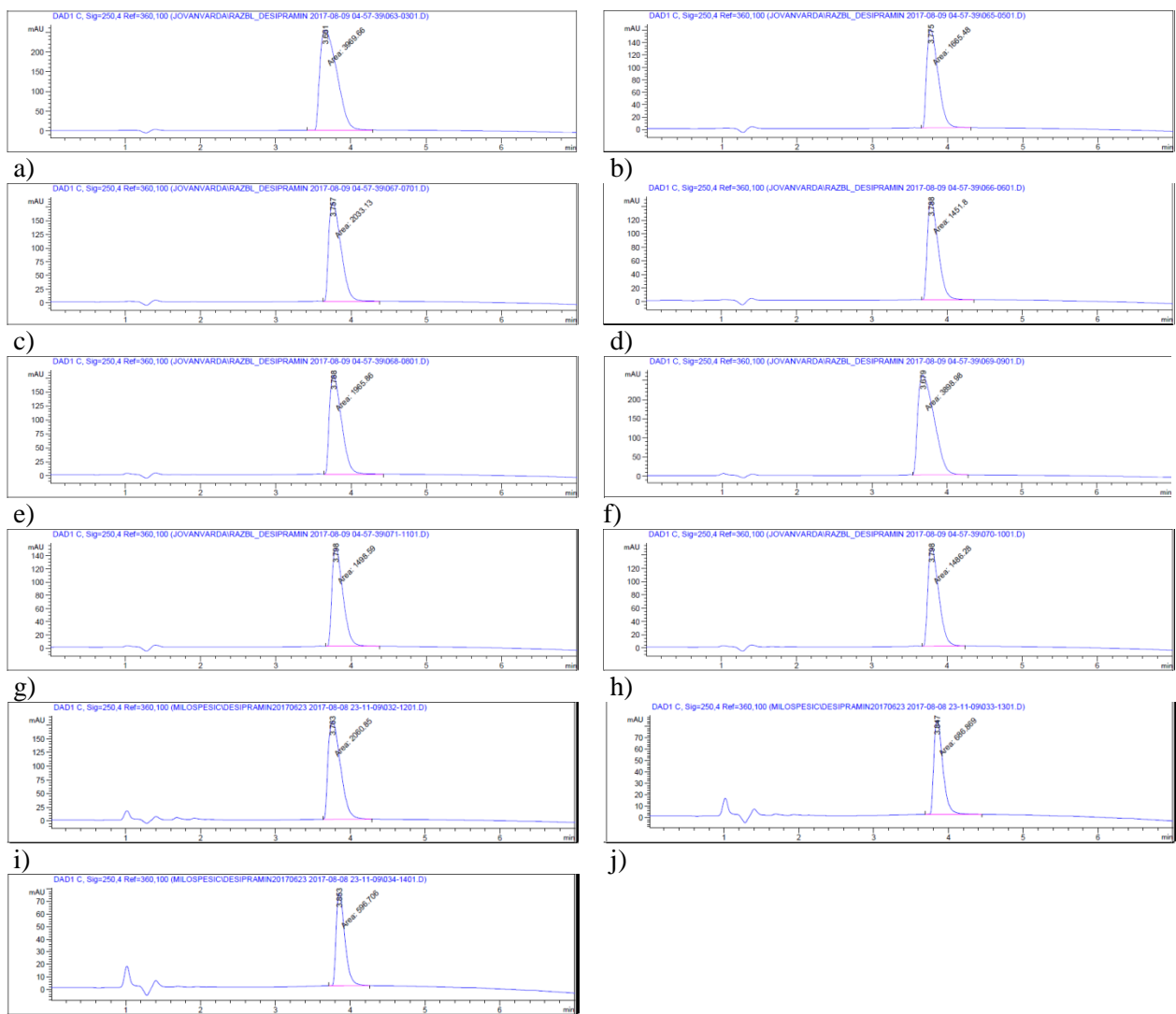


Figure S1. Equilibration of samples OM23 (pH 8.03) and OM13 (pH 7.41) at 25°C and 50% RH: (a) Moisture desorption by OM23 during equilibration at 25°C/50% RH, (b) TGA scan of OM23 after equilibration showing the total moisture content, (c) moisture sorption by OM13 during equilibration at 25°C/50% RH, and (d) TGA scan of OM13 after equilibration showing the total moisture content



k)

Figure S2. HPLC Chromatograms for Set 3 samples at different pH values:

- | | |
|--------------------------------------|--------------------------------------|
| a) Sample 1 – pH 3.99, diluted 100×; | b) Sample 2 – pH 4.73, diluted 60×; |
| c) Sample 3 – pH 5.19, diluted 40×; | d) Sample 4 – pH 6.04, diluted 20×; |
| e) Sample 5 – pH 6.69, diluted 10×; | f) Sample 6 – pH 7.14, diluted 4×; |
| g) Sample 7 – pH 7.79, diluted 10×; | h) Sample 8 – pH 9.64, diluted 10×; |
| i) Sample 9 – pH 10.08, diluted 2×; | j) Sample 10 – pH 11.00, diluted 2×; |
| k) Sample 11 – pH 11.47, diluted 2×. | |

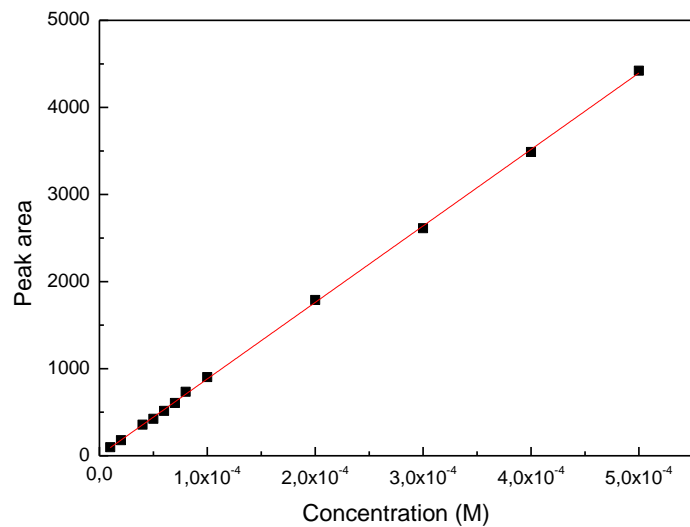


Figure S3. Calibration diagram for desipramine (concentration range 1.00×10^{-5} – 5.00×10^{-4} M) Linear fit:
Peak area = $8.7829 \times 10^{-6}c + 4.4574$