Supplementary Data, Methods and Results for:

The topography of simulated intestinal equilibrium solubility.

Claire Dunn, Jeremy Perrier, Ibrahim Khadra, Clive G. Wilson, Gavin W. Halbert.

Strathclyde Institute of Pharmacy and Biomedical Sciences,
University of Strathclyde,
161 Cathedral Street,
Glasgow, G4 0RE,
United Kingdom.

Abbreviations:
4CMD: 4-Component Mixture Design: NATC: sodium taurocholate; SPC: soya phosphatidyl choline; GMO: glyceryl mono-oleate; SO: sodium oleate.

Introduction

This supplementary file contains a range of source and method data along with results related to the above noted submission.

Source Data

Table 1 provides some basic physicochemical information on the three drug compounds employed within the four component mixture design.

Analytical Method Information

Table 2 provides information on the three HPLC methods employed to analyse the equilibrium solubility of the drugs in the media after incubation.

Additional Results

The results have been provided as supplementary data based on reviewer comments. Please read the main manuscript for a detailed explanation.

Figure 1 provides data from the 4CMD matrix presented as equilibrium solubility displayed in relation to the number of amphiphiles present in the measurement system. Data for carvedilol and fenofibrate are presented here. Whilst these figures are similar to the indomethacin results in the main manuscript of note is that the pH driven effect for indomethacin is not evident for either drug.

Figure 2 provides data on the equilibrium solubility of the center points within each 4CMD matrix arranged either with increasing total amphiphile concentration or pH. Data for carvedilol and fenofibrate are presented here. These figures are different to the indomethacin results in the main manuscript with subtle variations related to the solubility behaviour with respect to drug and total amphiphile concentration or pH. For example the impact of sodium oleate ionisation on the solubilisation of carvedilol is evident in Figure 2a top row but a similar effect is missing for fenofibrate. In addition for fenofibrate the in several systems the general rank order of the points is constant indicating that the system is exhibiting scalable solubility behaviour.

Figure 3 provides the calculated standardised effect values for the individual amphiphiles and amphiphile combinations on equilibrium solubility. See the main manuscript for a full explanation but of note is the visualisation of three way interactions for example for fenofibrate the results for the interaction of NATC with SPC at 77.5mM total amphiphile concentration is pH dependent, decreasing as pH increases.

Thank you for reading this material.

Table 1. Physicochemical properties of drugs measured in 4 Component Mixture Design

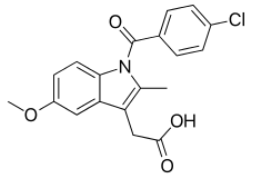
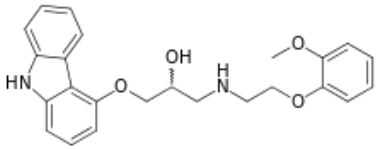
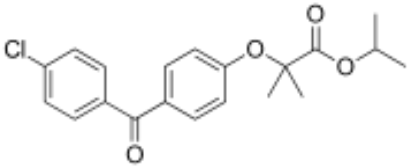
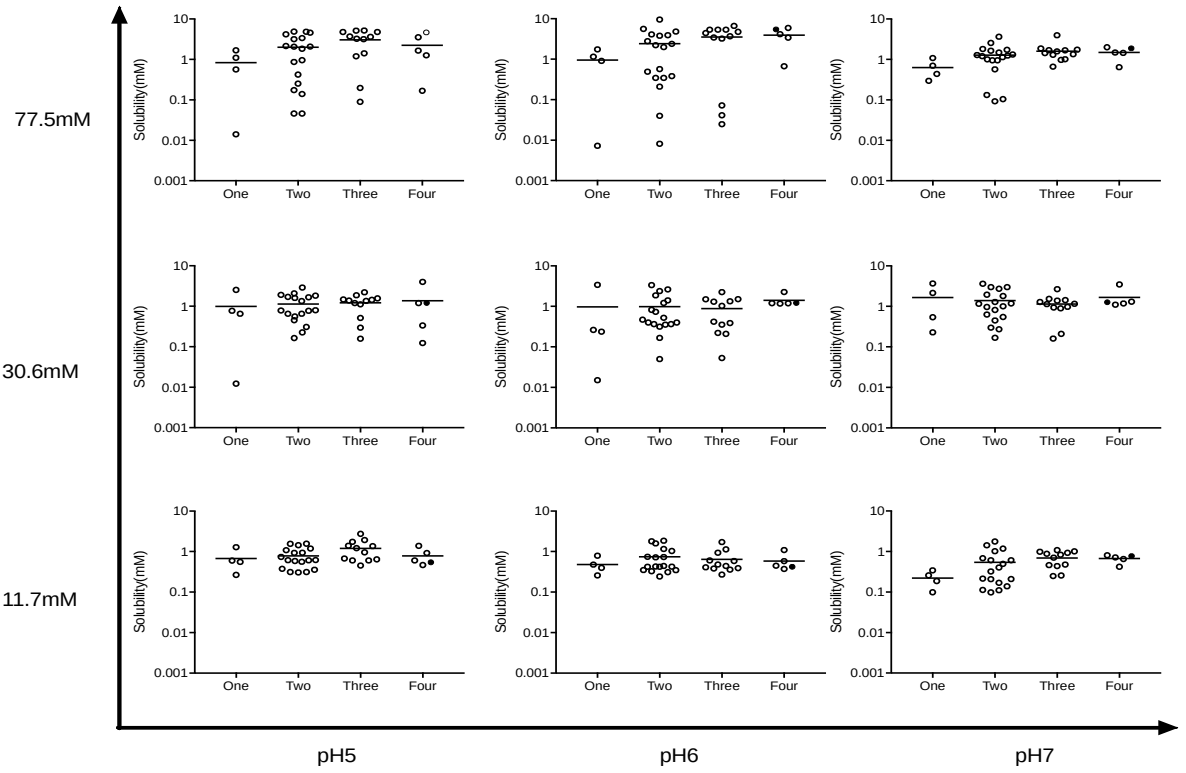
Compound	Category	Mw	log P	pKa	logD7/log D6.5	Structure
Indomethacin	Acid	357.8	3.11	4.5	0.89	
Carvedilol	Base	406.5	3.91	7.8	2.67/1.22	
Fenofibrate	Neutral	360.9	5.2	n/a	n/a	

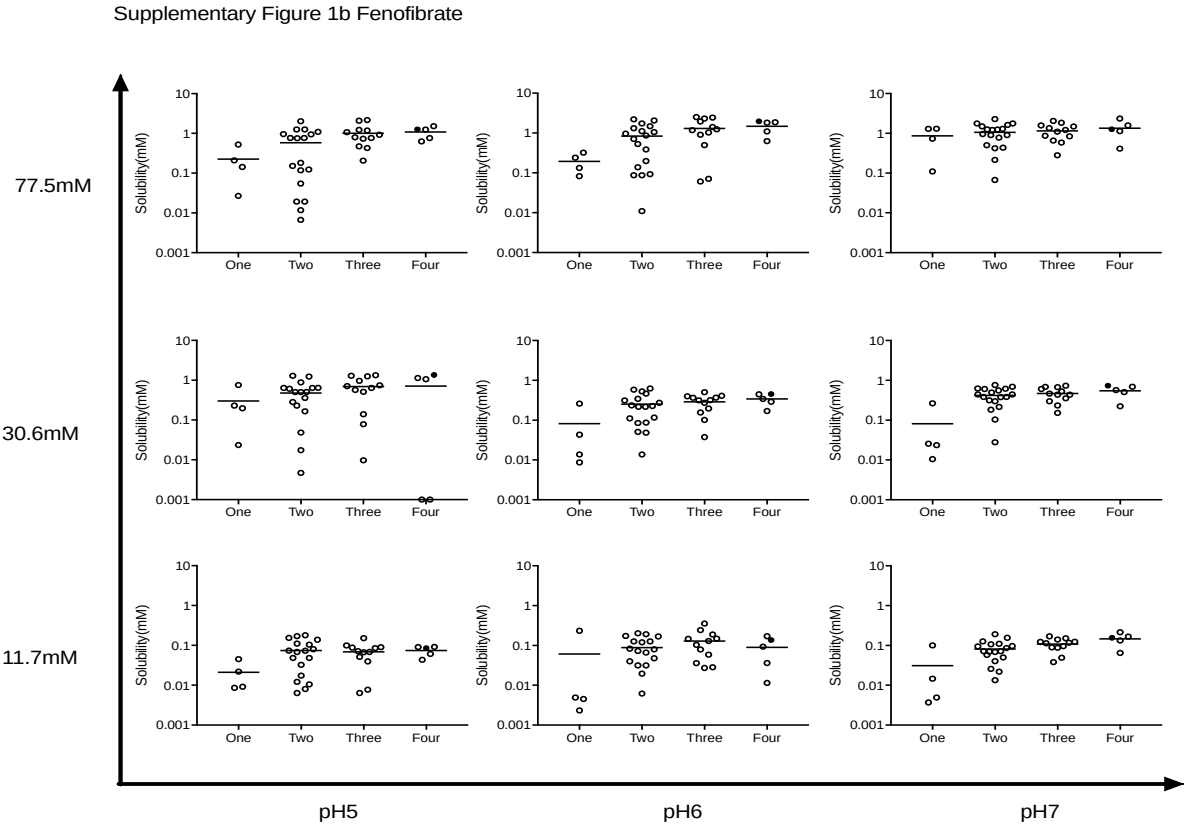
Table 2. HPLC Assay Conditions

Drug	Mobile phase	Column	Flow rate (ml/min)	Injection volume (µL)	Detection (nm)	Retention time (min)	r^2
Carvedilol	ACN : 0.05 M ammonium acetate (55 : 45) pH 4	2	1	10	243	2.2	0.9993
Fenofibrate	ACN : water (70:30 v/v)	1	1	100	291	3	1.0000
Indomethacin	Mobile phase A Ammonium formate 10 mM in H2O pH 3 Mobile phase B Ammonium formate 10 mM in ACN:H2O pH 3 (9:1 v/v)	3	1	10	254	0.84	0.998

Column 1: Speck & Burke ODS-H optimal 150x30 mm id 5 µm; Column 2: Agilent Polaris 5 C18-A 150X4.6 MM id 5 µm; ; Column 3 Hichrom ACE 3 C18 / 50 x 2.1 mm. ACN: Acetonitrile, TFA: Trifluoroacetic acid.

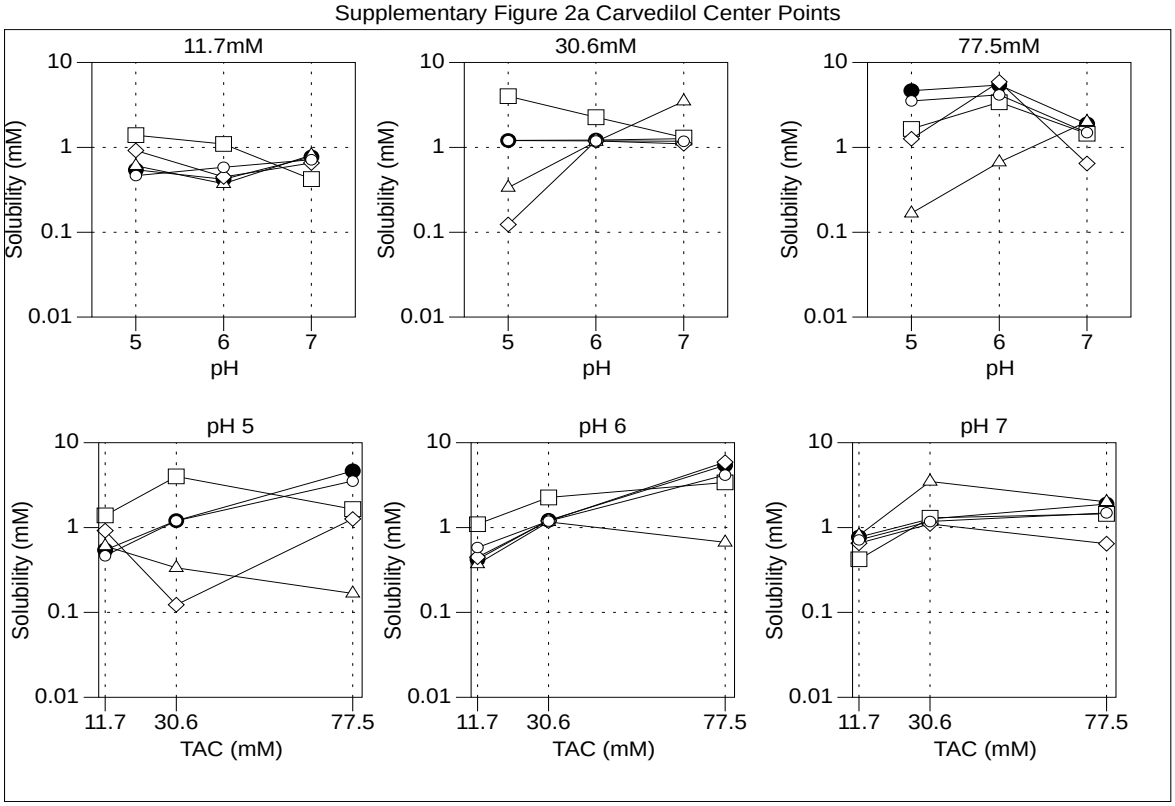
Figure 1. Influence of amphiphile number on measured equilibrium solubility.

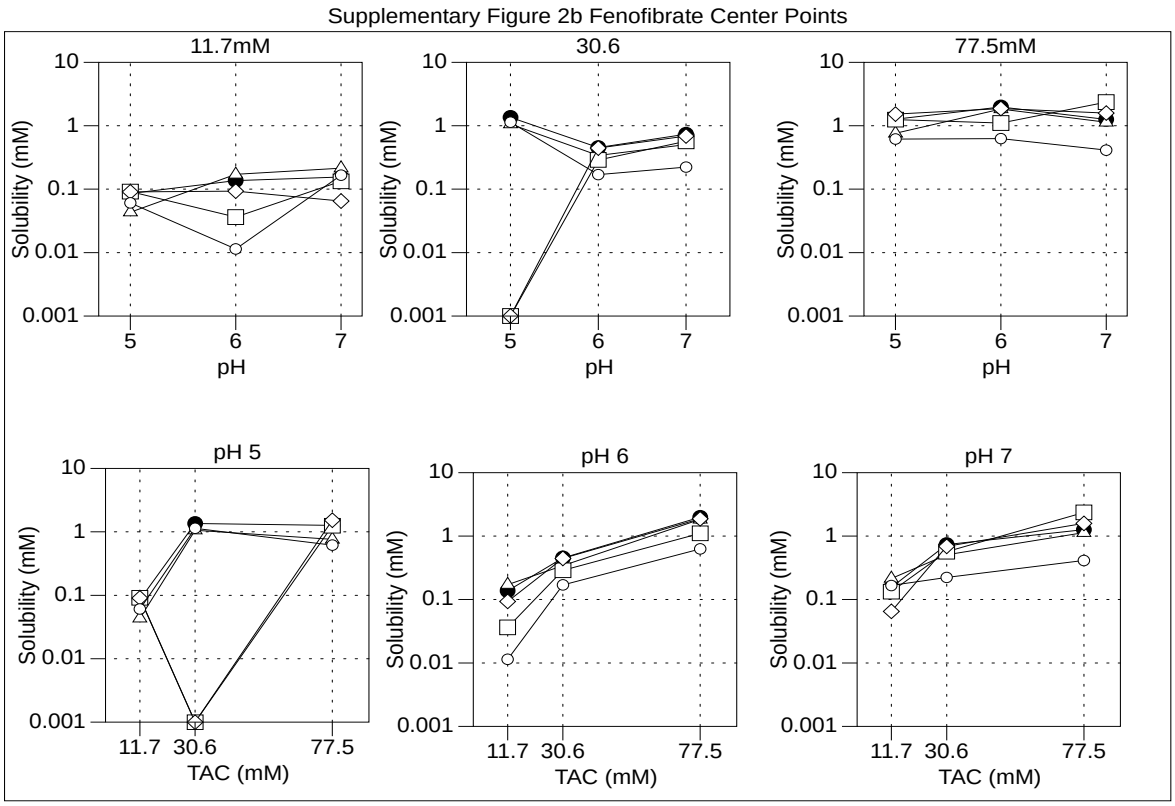




Legend: Equilibrium solubility data points determined during the 4 Component Mixture Design experiment presented as individual points based on the number of amphiphiles present. Bar – mean for each individual data set. ● In four amphiphile column = center point (See Table 1 Main Manuscript).

Figure 2. Internal point equilibrium solubility results.

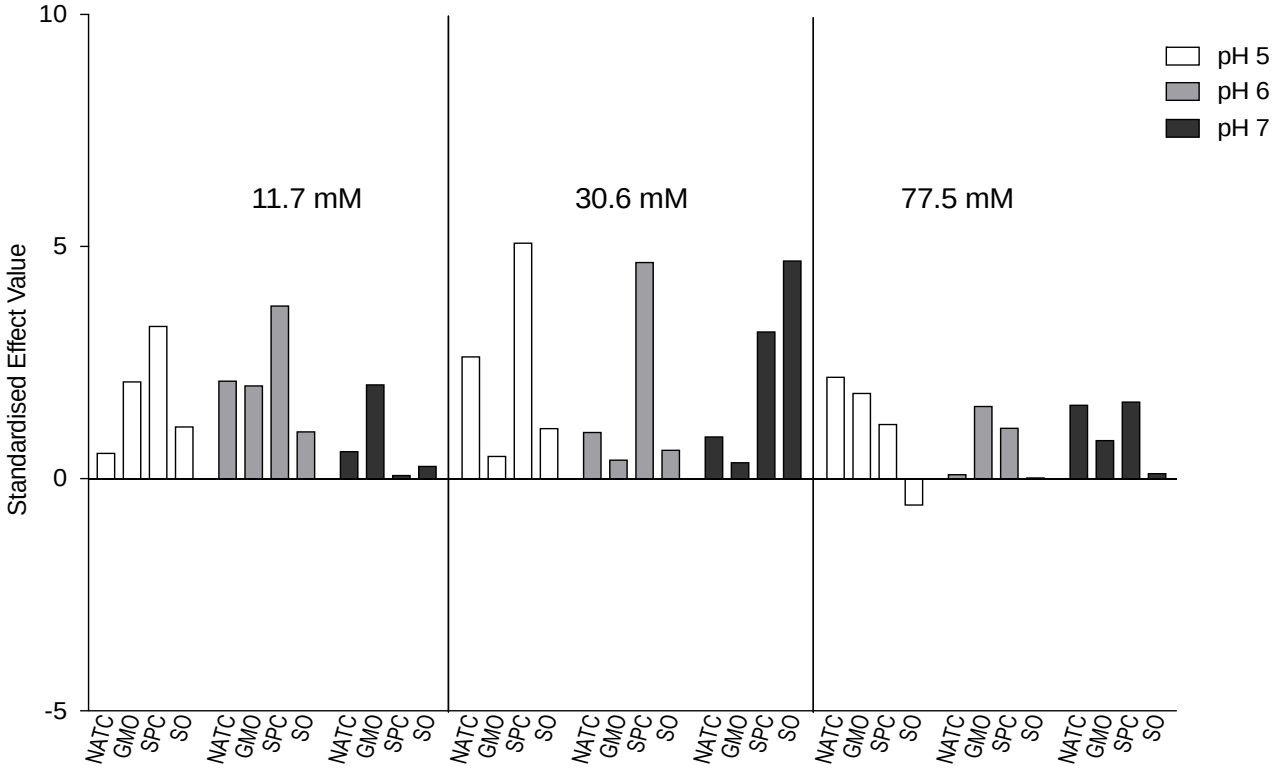




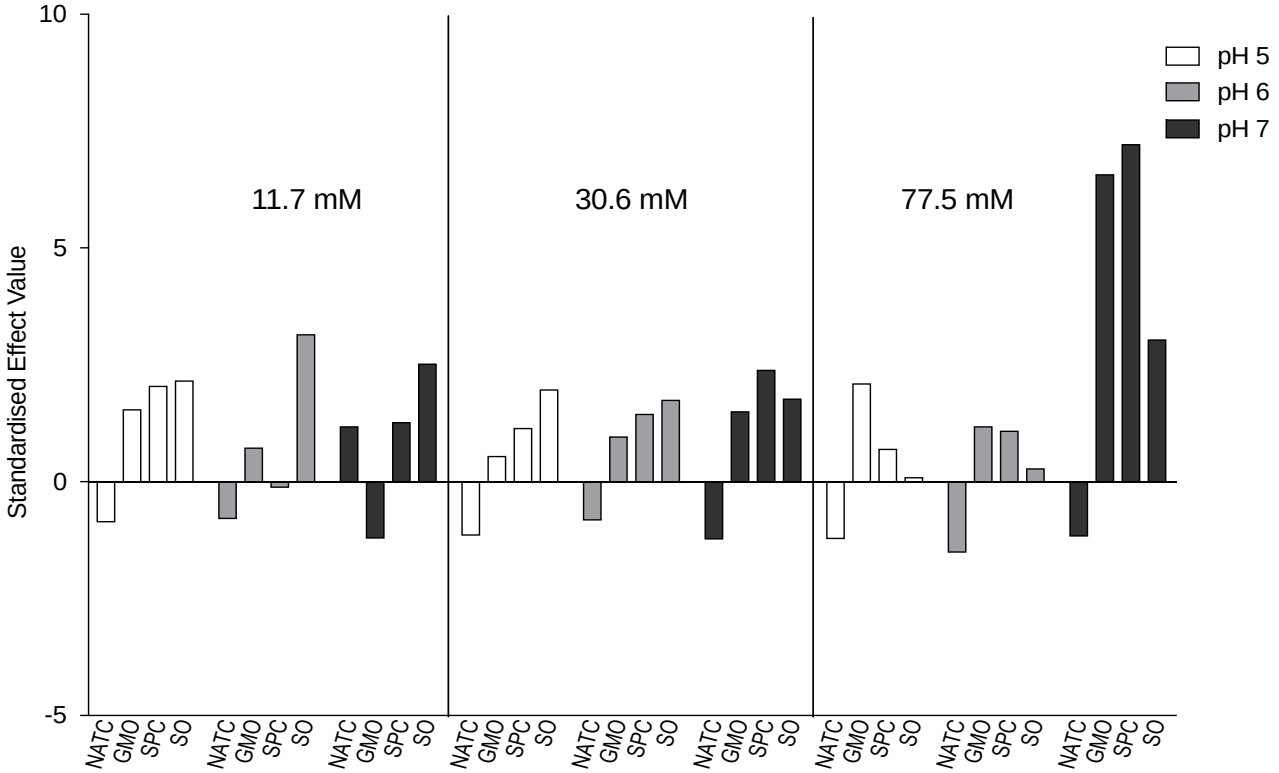
Legend: Equilibrium solubility data points plots determined during the 4 Component Mixture Design (4CMD) experiment. Data presented as a matrix based on measurement pH and total amphiphile concentration. Each individual plot represents the internal data points (See Table 1 Main Manuscript) from a 4CMD experiment grouped either by measurement pH or total amphiphile concentration. NB The surface data points are not included in this analysis. ● Center point; **O** High NATC; △ High SO; ◇ High GMO; □ High SPC.

Figure 3. Standardised effect values for individual amphiphiles and two amphiphile interactions.

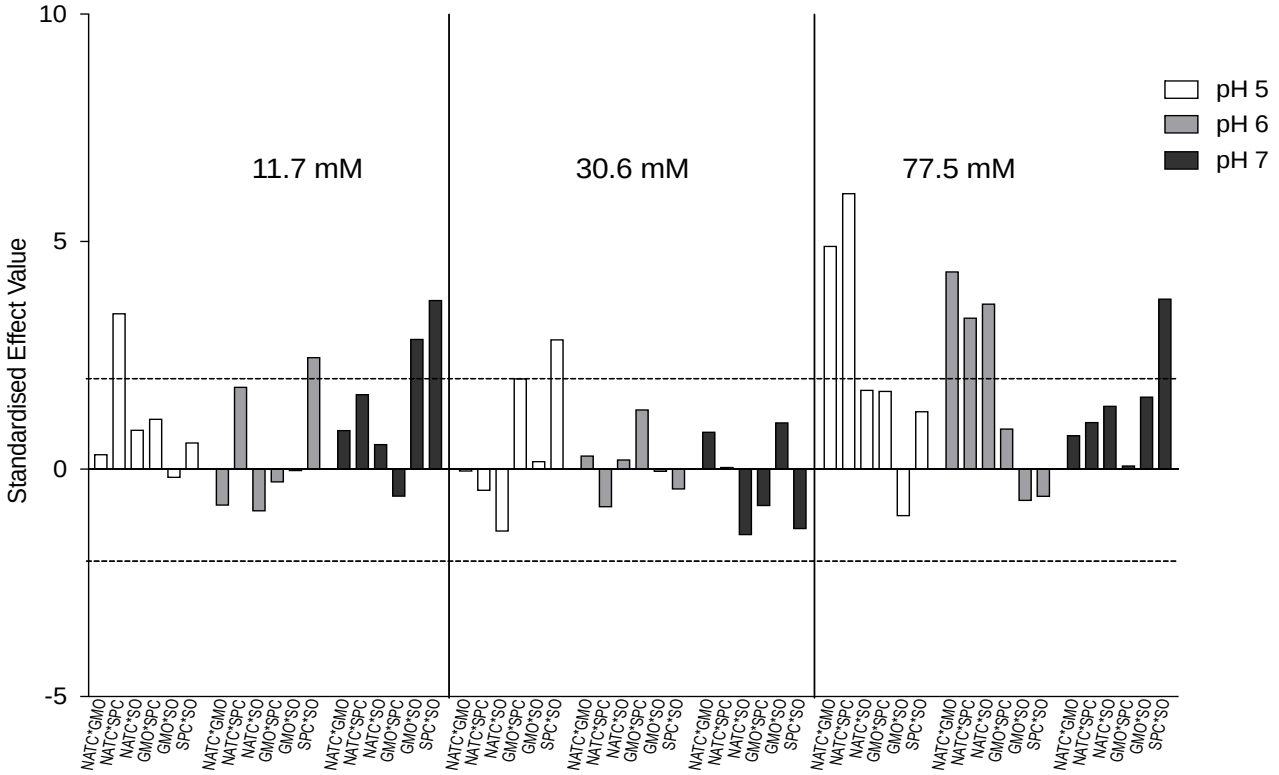
Supplementary Figure 3a Carvedilol single standardised ef fect values



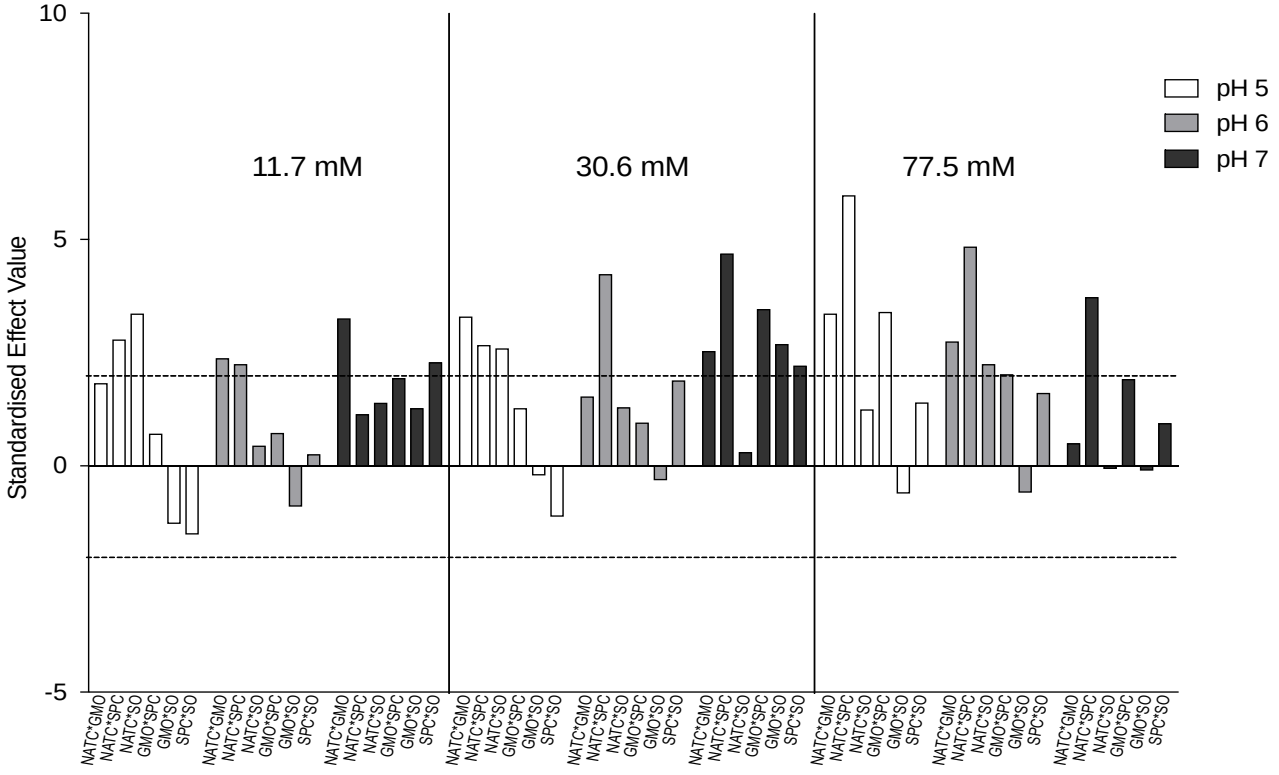
Supplementary Figure 3b Fenofibrate single standardised ef fect values



Supplementary Figure 3c Carvedilol two amphiphile interaction standardised ef fect values



Supplementary Figure 3d Fenofibrate two amphiphile interactions standardised ef fect values



Legend: Standardised effect value for individual amphiphiles and amphiphile combinations calculated by dividing coefficient with standard error, dashed line indicates p-value ($p > 0.05$). Due to model limitations no p-value generated for single amphiphile terms only a standardised effect value. Bars > 0 indicate a positive solubility effect, bars < 0 a negative solubility effect.