*p*DISOL-X™ software

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Lidocaine phosphate solids obtained from solubility experiment in Sörensen buffer (Ref. 3).

- ❑ **COCRYSTAL or SALT solubility-pH refinement, simulation, & assay design**
- ❑ **automatic solubility equation generator**
- ❑ **automatic electrode compensation for extreme ionic strength**
- ❑ **COCRYSTAL eutectic pH analysis; dimers, trimers, ..., micelles; complexes; amorphous, "supersaturation" effects; buffer interferences assessed**
- ❑ **mechanistic dissolution-pH kinetics (convective diffusion & simultaneous chemical reaction theory)**
- ❑ **rotating disk (Wood) & spherical particle (Wang-Flanagan) models**
- ❑ **calculation results exportable to Microsoft® Excel for customized plots**

- • ***p*DIS**OL-X concerns the analysis of DISSOLUTION-pH, taking into account the solubility, ionization constants, stirring rate, weight of solid, buffer capacity, etc., based on microspecies simulation of concentration gradients in the aqueous boundary layer (ABL), using a biophysical model extension from the methods described by Mooney-Stella (1980s) & Wang-Flanagan (1990s). Partial differential equations are solved *analytically*, for ultra-stable (& fast) calculations.

- • ***p*DISOL**-X concerns the analysis of SOLUBILITY-pH: solubility product for salts & COCRYSTALS, intrinsic solubility, sub-micellar aggregation (dimers, trimers, tetramers…), complexation – refinement & simulation. All species, including buffer components, are used in model calculations. Precise ionic strength, buffer capacity, and osmolarity are calculated at each point.

SOLUBILITY-pH.
Drug salt characterization is important in preparation of effective oral formulations. Salt solubility is a conditional constant, taking on different values according to the concentrations and types of reactants used. Lab-to-lab comparisons can be challenging, potentially leading to conflicting interpretations of *in vitro* dissolution measurements in formulation development.

- • Salt solubility measurement is usually carried out in concentrated solutions, with ionic strength, *I*, often exceeding 1 M.

- • COCRYSTAL log S-pH can be challenging to interpret in the pH range of eutectic stability.

- • Ionic activity coefficients are poorly controlled and cannot be accurately predicted by the simple Debye- Hückel equation.

- • pH electrode calibrated in buffers with *I* = 0.1 M may not be accurate at high ionic strengths due to excessive junction potentials.

- • The salt solubility depends on drug concentration & on that of counterion with which the charged drug precipitates. The counterion may originate from the buffer used or other unsuspecting solution additives.

- • Surface-active compounds can form micelles, self-associated aggregates (dimers, trimers, oligomers, etc.), or complexes with buffer species or other solution additives.

- • pH dependence of salt formation can be subtle, especially if the drug is surface active.

Deep Expertise at your Fingertips

The solubility and dissolution components of *p*DISOL-X are state-of-the-art tools for processing pH-dependent data of ionizable drug compounds, whether the molecules are extremely low-soluble, or prone to strong surface activity, or to binding to surfactants or complexing agents, or to self-aggregation.
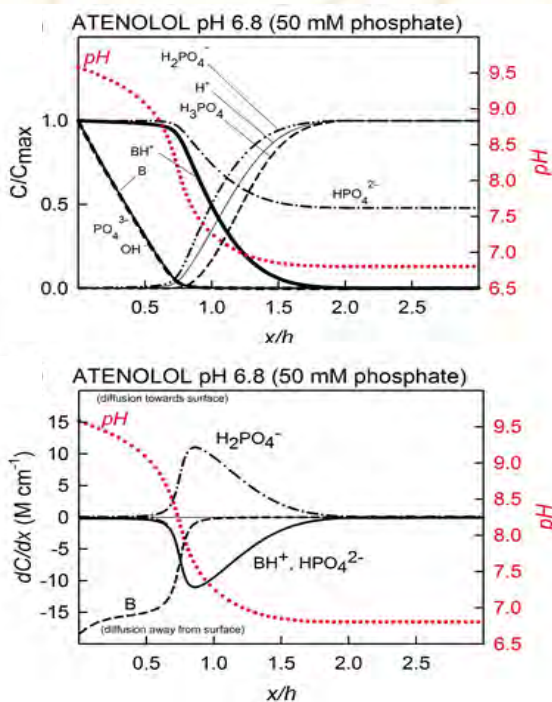

Fig 1. Simulated CDR speciation plots for atenolol in pH 6.8 buffer, at distances from surface of dissolving solid (in thickness of aqueous boundary layer, ABL, units): (top) relative concentrations of all species in the ABL; (bottom) concentration gradients, dC/dx, of all species in the ABL. Note that the surface pH is 9.5. (Adapted from Ref. 1.)

DISSOLUTION-pH.
Detailed simulation of the rate of dissolution of ionizable drugs, based on the convective diffusion & simultaneous chemical reaction (CDR) model complements the solubility part of *p*DISOL-X. The model incorporates microspecies mass balance & the Vinograd-McBain electric field treatments, & aspires to put the finishing touches to the pioneering works of Higuchi *et al.* (1958), Mooney-Stella *et al.*(1981), McNamara-Amidon *et al.* (1986).

- • Two CDR data simulations are available: (a) rotating disk intrinsic dissolution rate (disk IDR) and (b) Wang-Flanagan spherical particle intrinsic dissolution rate (particle-IDR) models.

- • The rigorous CDR kinetics model is most helpful in early mechanistic applications of IDR, where compounds are studied as compacted solid rotating disks or suspended powders of the pure compound.

- • Concentration-time profiles as a function of pH, buffers, salt, complexation and self-aggregation are considered.

- • Concentration-position profiles of all species in the aqueous boundary layer (ABL), including solid species, are also considered under the above conditions.

- • Effect of buffer capacity on intrinsic dissolution rate is analyzed.

Examples of Solubility-pH Analysis using *pDISOL-X*

KETOPROFEN & sodium lauryl sulfate

37°C

2.0% SLS
1.0% SLS
0.5% SLS
0% SLS

pK_a 4.69 ± 0.11
pK_a^{SLS} 6.69 ± 0.30
S_O 245 ± 47 μg/mL
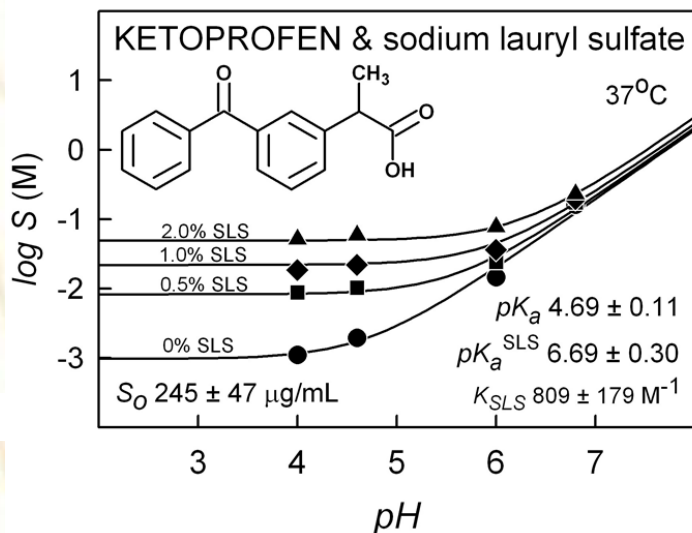K_{SLS} 809 ± 179 M^{-1}

Fig 2. The solubility behavior of ketoprofen at 37 °C in pH 4.0, 4.6, 6.0, and 6.8 buffer media, in the presence of 0, 0.5, 1.0, and 2.0% w/v SLS. (Adapted from Ref. 2).
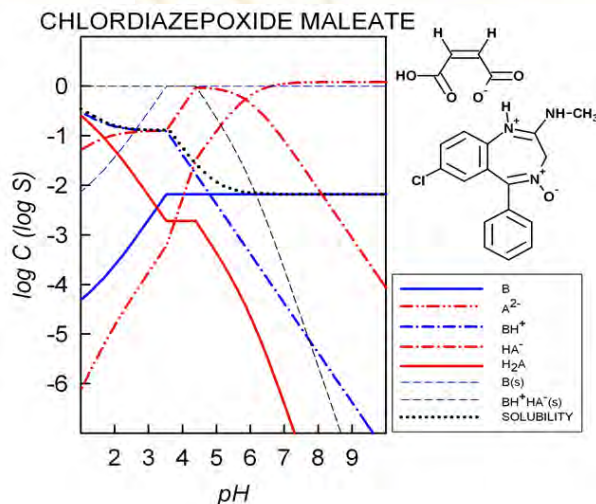

CHLORDIAZEPOXIDE MALEATE

B
A^{2-}
BH$^+$
HA$^-$
H$_2$A
B(s)
BH$^+$HA$^-$(s)
SOLUBILITY

Fig 3. The complete speciation profile for chlordiazepoxide maleate, illustrating how complex the parallel interactions can be. This example illustrates that mathematical understanding of ionic equilibria is important for the correct interpretation of such complex reactions. (Adapted from Ref. 2.)
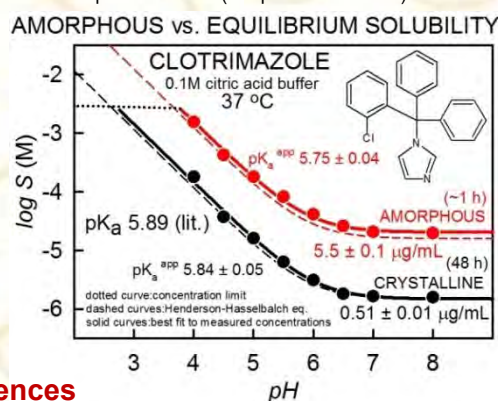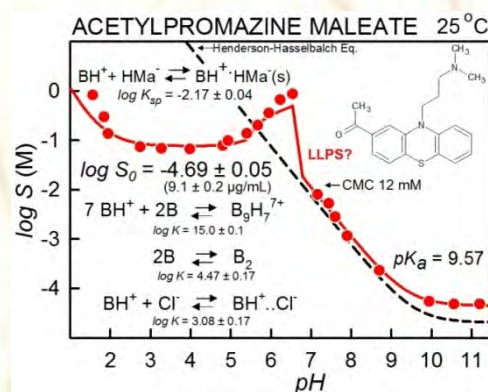

ACETYLPROMAZINE MALEATE 25 °C

Henderson-Hasselbalch Eq.
BH$^+$+ HMa$^-$ ⇌ BH$^+$·HMa$^-$(s)
$log K_{sp}$ = -2.17 ± 0.04
$log S_0$ = -4.69 ± 0.05
(9.1 ± 0.2 μg/mL)
LLPS?
CMC 12 mM
7 BH$^+$ + 2B ⇌ B$_9$H$_7^{7+}$
$log K$ = 15.0 ± 0.1
2B ⇌ B$_2$
$log K$ = 4.47 ± 0.17
BH$^+$ + Cl$^-$ ⇌ BH$^+$..Cl$^-$
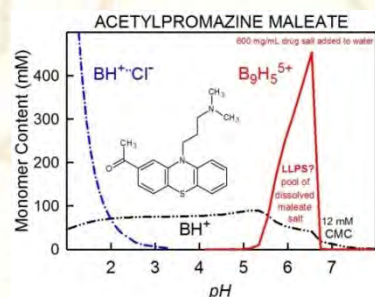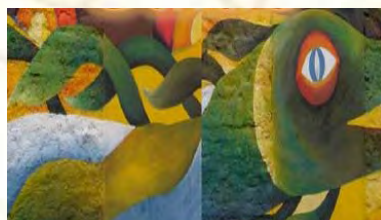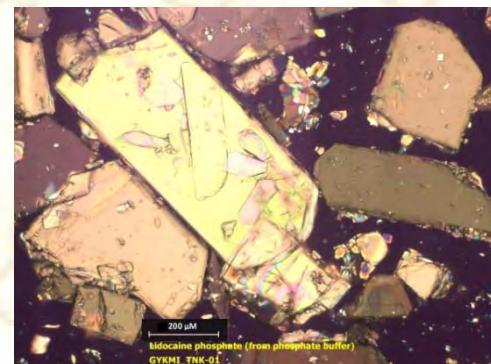$log K$ = 3.08 ± 0.17
pK_a = 9.57

Fig 5. Analysis of a phenothiazine derivative forming a micelle while precipitating as the maleate salt and as the free base. Based on data from Liu S-T, Hurwitz A. The effect of micelle formation on solubility and pK$_a$ determination of acetylpromazine maleate. *J. Colloid Int. Sci.* **1977**, *60*, 410-413.

AMORPHOUS vs. EQUILIBRIUM SOLUBILITY

CLOTRIMAZOLE
0.1M citric acid buffer
37 °C
pK$_a^{app}$ 5.75 ± 0.04
pK$_a$ 5.89 (lit.)
pK$_a^{app}$ 5.84 ± 0.05
(~1 h)
AMORPHOUS
5.5 ± 0.1 μg/mL (48 h)
CRYSTALLINE
0.51 ± 0.01 μg/mL
dotted curve:concentration limit
dashed curves:Henderson-Hasselbalch eq.
solid curves:best fit to measured concentrations

Fig 4. Analysis of data from Indulkar AS, Box KJ, Taylor R, Ruiz R, Taylor LS. pH-dependent liquid–liquid phase separation of highly super-saturated solutions of weakly basic drugs. *Mol. Pharmaceutics* **2015**.

ACETYLPROMAZINE MALEATE
600 mg/mL drug salt added to water
BH$^+$·Cl$^-$
B$_9$H$_5^{5+}$
LLPS?
pool of dissolved maleate salt
BH$^+$
12 mM CMC

*p*DISOL-X References

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Please note: publication-quality customized plots shown here were drawn using SigmaPlot ® (Systat Software, Inc.), based on *p*DISOL-X calculation results exported to Microsoft® Excel.

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regional distributor

lidocaine phosphate (from phosphate buffer)
GYKMI_TNK-01
200 μM