WHITE PAPER

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pH-Solubility diagrams and their usefulness in characterization of salts of poorly soluble drug substances

For weak acids or bases, *the aqueous solubility of a salt of the ionized form is often much higher than that of the free (acid or base) form. This fact is utilized when designing formulations of active pharmaceutical ingredients (APIs), where it is often found that the use of salt forms gives highly improved bioavailability compared to the free form. However, since the true solubility of a substance is always limited by the solubility of the most stable form at a certain set of conditions, careless use of salt forms of drug substances may result in unwanted situations. In order to avoid unpleasant surprises, care should be taken to identify the species and equilibria that influence the effective solubility of an API in a relevant range of conditions.*

In this paper, the construction of proper solubility diagrams will be discussed. We will begin with a look at the simple case of a monoprotic base with a non-titrating counterion, then continue with a brief discussion on the sometimes substantial influence of background salt, and finish off by considering the solubility of salts carrying a titrating counterion.

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There are sometimes good reasons for using a salt of an active compound

When facing the task of formulating an active pharmaceutical ingredient (API), there are sometimes strong incentives for using a *salt* of the active component, rather than the free (acid or base) form. For instance, it is often found that poor bioavailability, which is nowadays an oft-encountered problem with new API candidates, can be improved by administering the drug as a salt. The improved bioavailability of a salt is related to the typically much better solvation of ions, which allows for fast and efficient dissolution. However, as will be elaborated in this paper, the *thermodynamic* solubility of a given compound is independent of the solid form administered.

The use of a salt form of an API does often have the additional advantage of yielding improved solid-state properties. Whereas the free forms of organic acids or bases are sometimes difficult, or impossible, to produce in anything else than an amorphous form, salts are typically much easier to crystallize. An amorphous solid may show batch to batch variation in production, be difficult to handle, or be prone to changes in character over time. Thus, amorphous forms are generally avoided. Crystalline solids, on the other hand, are typically easier to handle and allow for more straightforward characterization (which is critical for an appropriate quality control). Also in cases where the free form of an API does show a crystalline form, there might be drivers for the selection of a salt, for instance if the compound shows high hygroscopicity or poor flow properties.

However, there are also reasons to be cautious

As was alluded to above, it is of critical importance to realize that the improved solubility of a salt (relative to the free form) may represent a transient, kinetically controlled situation rather than a thermodynamically stable state. For instance, depending on the pK_a value(s) of the substance in question relative to the pH at use (in a formulation or *in vivo*) the free form may be the thermodynamically stable one. In such a case one will, given sufficient time, have a transformation from the ionized form to the free form. In the commonly encountered situation where the free form has lower solubility than the salt, this will lead to precipitation of the active substance (a process that is sometimes, incorrectly, referred to as salt disproportionation). The situation may be further complicated by, for instance, transitions between polymorphs, formation of hydrates with even lower solubility, and/or precipitation of a poorly soluble salt of a different ion present in the system.

Taken together, it is not uncommon that the form of an API one starts out with is in fact not the form governing the thermodynamic solubility of the substance. The transition to the thermodynamically stable form (or a metastable form of lower solubility than the administered one) may be, and often is, slow. However, sometimes transitions, and an associated precipitation, may be fast or sudden, and the stability of metastable states may be strongly dependent on the conditions. Thus, careless use of salt forms of APIs may result in unwanted situations. In order to avoid unpleasant surprises, care should be taken to identify the species and equilibria that influence the effective solubility of the compound in a relevant range of conditions. In the following, the construction of proper solubility diagrams will be described, starting with the simple case of a monoprotic base with a non-titrating counterion.

The basic principles of pH-solubility diagrams

Assume that we have an API, B. Let B be a weak base that is a solid at room temperature. The dissolution of B in its free form, i.e.

$$B(s) \rightleftharpoons B(aq) \tag{1a}$$

can be characterized by its intrinsic solubility, which is described by the solubility constant, K_{sB}, according to

$$K_{sB} = [B] \tag{1b}$$

The dissolved free base is in equilibrium with its protonated acid form HB^+ according to the standard expressions

$$HB^+ \rightleftharpoons H^+ + B \tag{2a}$$

and

$$K_{aB} = \frac{[H^+][B]}{[HB^+]} \tag{2b}$$

where K_{aB} is the acid dissociation constant of HB^+.

The effective solubility of B, in terms of the total concentration of B in solution, C_B, is described by

$$C_B = [B] + [HB^+] \tag{3}$$

The combination of Equations 1b, 2b, and 3 gives the following expression for the variation in C_B with the proton concentration.

$$C_B = K_{sB}\left(1 + \frac{[H^+]}{K_{aB}}\right) \tag{4}$$

If we assume that HB^+ has a pK_a, pK_{aB}, of 4 and an intrinsic solubility of 0.1 mM, and these values are inserted into Equation 4, the pH-solubility profile for B can be plotted, see Figure 1.

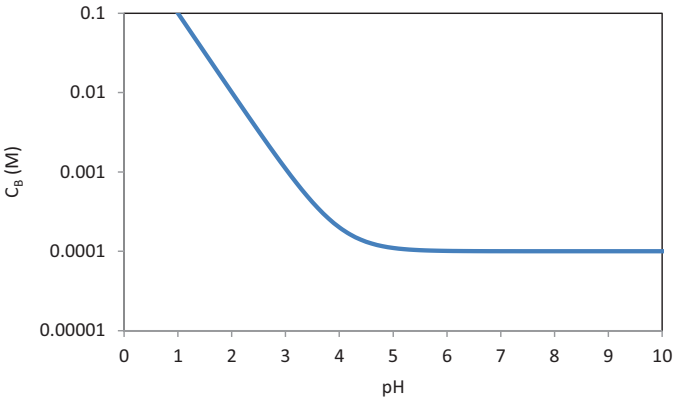

Figure 1. *The pH-solubility profile for a weak base* B *with a* pK_a *of 4 and an intrinsic solubility of 0.1 mM.*

Now assume that we prepare a salt of B (strictly speaking a salt of the acid form of B, i.e. HB^+), with a simple, non-titrating counterion, X^-. "Non-titrating", in this context, means that the counterion X^- does not have a relevant pK_a, and thus will be charged independent on pH. Pertinent examples are provided by the halide ions chloride, bromide, and iodide. The solubility of the salt can be expressed by

$$(HB^+)\,X^-\,(s) \rightleftharpoons HB^+\,(aq) + X^-\,(aq) \tag{5a}$$

and the associated solubility product by

$$K_{sX} = [HB^+]\,[X^-] \tag{5b}$$

From the combination of Equations 2b, 3, and 5b, and the assumption that $[X^-] = C_B$ (i.e. that no X^- is present in the dissolution medium prior to dissolution of our salt), one arrives at the expression

$$C_B = \sqrt{K_{sX}\left(1 + \frac{K_{aB}}{[H^+]}\right)} \tag{6}$$

which describes the solubility of $(HB^+)X^-$. The pH-solubility profile for $(HB^+)X^-$, according to equation 6, may look as shown in Figure 2.

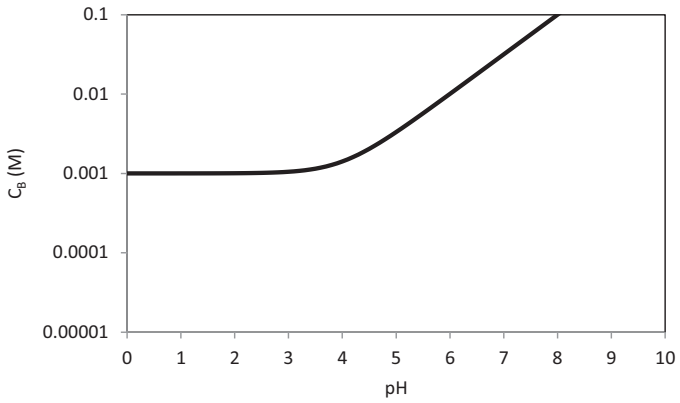

Figure 2. *The pH-solubility profile for a salt of the weak base* B *and a non-titrating anion* X^-*, as described by equation 6. The solubility product of the salt is* 1×10^{-6}.

However, the plot in Figure 2 does not tell the whole story about the solubility of the salt. Since Equilibrium 5a, via Equilibrium 2a, is coupled to the dissolution of the free base according to Equilibrium 1a, the equilibrium value of C_B cannot be correctly described without also taking into account Equation 4. At a given pH, the form with the lowest solubility will be the thermodynamically stable one. The proper pH-solubility profile is shown in Figure 3. One can here see that the solubility of $(HB^+)X^-$ is actually dictated by the solubility product of the salt only at rather low pH. Above pH 3, and thus at physiological conditions, the deprotonated free base is the thermodynamically stable form in equilibrium with a saturated solution.

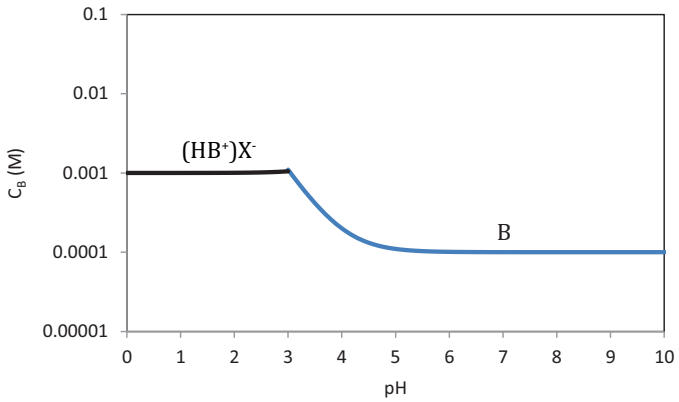

Figure 3. *The proper pH-solubility profile for a salt of the weak base* B *and a non-titrating anion* X^-*, where the solubility of the free base is taken into account. The black section of the trace refers to conditions where the salt form is the thermodynamically stable form in equilibrium with a saturated solution. In the blue section, the free base is instead the thermodynamically stable form.*

The sometimes drastic influence of background salt – consequences of the common-ion effect

As was stated above, the pH-solubility profile shown in Figure 3 is valid for the case where the condition $[X^-] = C_B$ holds. However, as a consequence of expressions 5a and 5b, the presence of background salt with X^- as the anion has an impact on the effective solubility of B. This is often referred to as "the common-ion effect". If one has, for instance, a certain concentration of a soluble salt M^+X^- in the solution (say NaCl, if X^- is Cl^-), its presence will cause a shift of Equilibrium 5a towards the left and, consequently, a decrease in the effective solubility of $(HB^+)X^-$. With the common-ion effect taken into account, the expression corresponding to Equation 6 will read

$$C_B = -\frac{[M^+]}{2} + \sqrt{\left(\frac{[M^+]}{2}\right)^2 + K_{sX}\left(1 + \frac{K_{aB}}{[H^+]}\right)} \qquad (7)$$

where the concentration of the background salt is expressed in terms of the concentration of its cation M^+.

As exemplified in Figure 4, one can, particularly for a salt with limited solubility, have a substantial reduction in the effective solubility even with a rather low concentration of background salt.

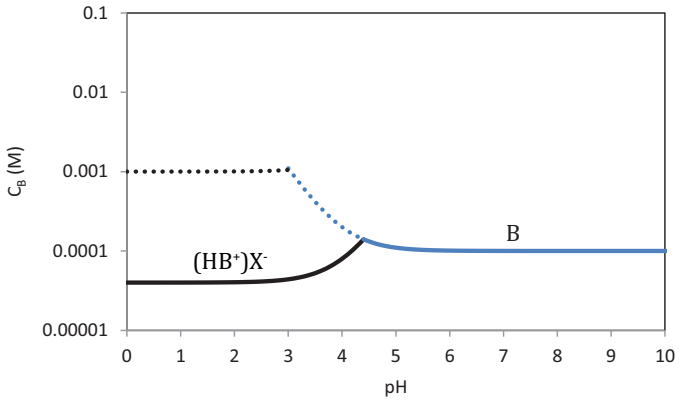

Figure 4. *The pH-solubility profile for* $(HB^+)X^-$ *in the presence of 25 mM of the soluble salt* M^+X^- *(solid lines) compared to the case without background salt (dotted black and blue and solid blue lines, i.e. the situation illustrated in Figure 3).*

The case of titrating counterions

In practice, a common situation is that the salt of an API has a counterion that, rather than being a simple, non-titrating ion like chloride, is the base form of a weaker acid. We denote such a salt $(HB^+)A^-$. In order to properly describe the solubility of $(HB^+)A^-$, we do not only have to take into account the solubility product of the salt (Equation 8) and the solubility of the free base (Equation 4), but also the corresponding equilibria for the acid HA, i.e. the acid dissociation equilibrium for HA and the coupled dissolution equilibrium for the free acid (Equilibria 9a and 10a, and the corresponding Equations 9b and 10b, respectively).

$$K_{sS} = [HB^+][A^-] \tag{8}$$

$$HA \rightleftharpoons H^+ + A^- \tag{9a}$$

$$K_{aHA} = \frac{[H^+][A^-]}{[HA]} \tag{9b}$$

$$HA(s) \rightleftharpoons HA(aq) \tag{10a}$$

$$K_{sHA} = [HA] \tag{10b}$$

By combination of the appropriate equations in a similar manner as described above, one will arrive at the expressions

$$C_A = K_{sA}\left(1 + \frac{K_{aHA}}{[H^+]}\right) \tag{11}$$

and

$$C_A, C_B = \sqrt{K_{sS}\left(1 + \frac{K_{aB}}{[H^+]}\right)\left(1 + \frac{[H^+]}{K_{aHA}}\right)} \tag{12}$$

for describing the solubilities of HA and $(HB^+)A^-$, respectively.

Using the principles described for $(HB^+)X^-$ above, the proper pH-solubility curve for $(HB^+)A^-$, which is illustrated in Figure 5, can be arrived at by comparing plots of expressions 4, 11, and 12.

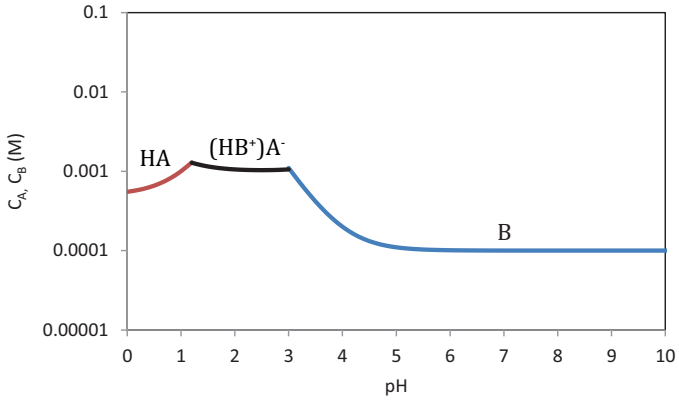

Figure 5. *The pH-solubility profile for a salt (with a K_{sS} of 1×10^{-6}) of a weak base B (with an intrinsic solubility of 0.1 mM and a pK_a of 4) and a weak acid HA (with an intrinsic solubility of 0.5 mM and a pK_a of 1). The black section of the trace refers to conditions where the salt $(HB^+)A^-$ is the thermodynamically stable form in equilibrium with a saturated solution. In the blue section, the free base B is the thermodynamically stable form, whereas in the red section of the curve, the acid form of the counterion, i.e. HA, is the solubility-limiting species.*

The importance of an appropriate experimental approach

From the above discussion it is clear that it can be absolutely critical to have a detailed insight into the pH-solubility profile for an API to be formulated. So how does one construct a proper solubility diagram for the substance at hand? What one needs to do first is to identify all equilibria that influence the effective solubility of the API. As is shown above, several equilibria may be at play even in a rather simple system. Then, one needs to obtain accurate values of the relevant pK_a and equilibrium solubilities. If experiments are carefully designed, the amount of experimental work required for the construction of an appropriate solubility diagram can actually be rather limited. For solubility values, it is very important to verify that the form controlling solubility at a certain set of conditions is indeed the form one is supposed to have. pK_a values should preferably be determined experimentally. There are several tools available for theoretical prediction of pK_a values, but, at least for complex molecules, the accuracy of the calculated values is often far from sufficient for the purpose. As can be understood from the above discussion, rather limited errors in the values of experimental data, as well as deviations in the conditions at which they are determined, can lead to substantial errors regarding the effective solubility of a substance.

CR Competence has extensive experience of formulation of poorly soluble active substances, including salt selection and the construction of solubility diagrams.

If you believe that our support can be helpful to your business, please contact:

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