Measuring the solubility of salts of basic drugs without first creating the salts

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Purpose

During drug development, chemists need to choose salts with optimum properties for bioavailability and formulation. An important property of salts is their solubility. Values are typically measured after first creating the salt in crystalline form. We sought to develop a method for measuring salt solubility without the need to prepare crystals of the salts.

Methods

A weighed sample of basic drug (or its water-soluble salt) together with a weighed quantity of the counter ion in free acid form are suspended in 10 mL of water. Provided the base and acid exceed their saturation limits, then as the pH is lowered below the pK_a of the weak base by adding aliquots of a strong acid such as HCl, some of the ionized base reacts with ions of the acidic counter-ion to form an insoluble salt. In effect, the suspended solid converts from the unionized form to the salt form, yet remains in suspension. If pH is adjusted slowly such that the system is always close to equilibrium, the conversion between the two solid forms happens at a single pH called pH_{max} whose value depends on the amount of weak base and weak acid present in the system as well as on the solubility of the salt, which in turn depends on the intrinsic solubility of the substance and its pK_a. Our new method measures pH_{max} , and the same apparatus also measures pK_a and intrinsic solubility.

Results

We measured the pK_a and intrinsic solubility of loperamide, and then measured pH_{max} of five loperamide salts, from which we determined their solubilities in units of mM. We observed that the salt solubilities decreased in the order mesylate, hydrochloride, besylate, benzoate and tosylate. We showed that the rank order of solubilities could be determined without needing values for pK_a and intrinsic solubility. We also showed that salicylate and acetate failed to produce reliable pH_{max} values and were unable to form salts with loperamide.

Conclusion

This new method successfully measures pH_{max} in saturated solutions of basic drugs with counter-ions, from which their salt solubility can be determined.

Picture shows SiriusT3 instrument (single-sample version). This instrument is suitable for measuring pH_{max} values using the methods described here, in solution volumes of 1.5 mL and low mg sample weights.

References

1. Streng, W. H., Int. J. Pharm. 1999, 186, 137-140.
2. Box, K. J.; Comer, J. E., Curr. Drug Metab. 2008, 9 (9), 869-78.

Theory of measurement

Weak bases are least soluble when unionized at high pH. Provided the ionized form is in solution, the relationship between solubility and pH is summarised by the Henderson-Hasselbalch equation, which shows that the solubility is equal to its intrinsic solubility at pH values above its highest pK_a, and that solubility vs. pH increases logarithmically at pH values below its pK_a. This is shown in Figure 1.

Some bases form poorly soluble salts with acidic counter-ions. As the pH of a solution containing the suspended salt is raised, the suspended salt converts to the unionized form, yet remains in suspension. If pH is adjusted slowly such that the system is always close to equilibrium, the conversion between the two solid forms happens at a single pH called "pH_{max}".

The value of pH_{max} depends on the solubility of the salt. It also depends on the weight of base and counter-ion present in the system, solution volumes, the intrinsic solubility of the substance (S_0) and the pK_as of the base and the counter-ion, all of which can be measured. Thus, if pH_{max} could be measured, the solubility of the salt could be determined.

Streng [1] showed that by using pH_{max}, aqueous pK_a , intrinsic solubility S_0 and concentration of the anion $[X^-]$, it is possible to derive the salt solubility product, K_{sp} (defined as $[X^-][BH^+]$) using the equation:

$$pK_a + \log S_0 + pK_{SP} = pH_{max} - \log[X^-]$$

The result reported from the assay may be solubility product K_{sp}, or it may be $[BH^+]$ at the appropriate pH. Figure 2 shows solubility of loperamide vs. pH measured for salts with a various counter-ions. In this graph the solubility logS refers to $\log S_0$ at high pH and $\log[BH^+]$ at low pH. Note that it is also possible to rank solubilities by measuring pH_{max} without knowing their pK_a or intrinsic solubility.

Solubility results

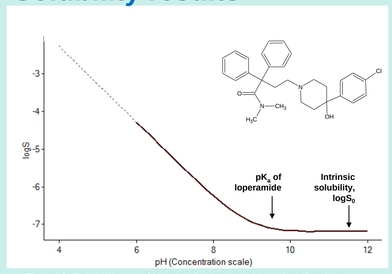

Figure 1. Solubility vs. pH profile for loperamide using Henderson Hasselbalch equation, and a measured $\log S_0$ value of -7.13 [2].

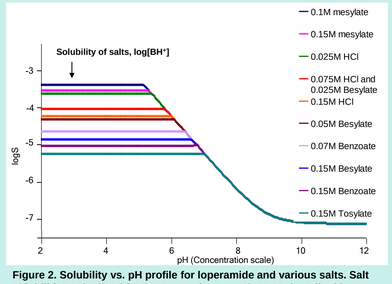

Figure 2. Solubility vs. pH profile for loperamide and various salts. Salt solubilities calculated from measured pH_{max} values as described here.

Measuring pH_{max}

Measurements can be made using the SiriusT3 instrument.

The substance must be a free base or a water-soluble salt. A sample is weighed into a vial, together with a weighed quantity of the counter-ion. Deionized water is then added. For a successful experiment, a precipitate must be present at the start of the experiment. The solution is then titrated with a strong base (e.g. 0.5 M KOH solution). The pH is measured and then plotted as a function of the volume of added KOH solution. Figures 3 and 4 show an example, loperamide in the presence of benzenesulfonic acid.

Below pH_{max}, data points can be collected quickly. During this stage the loperamide is in ionized form. Addition of KOH raises the pH and converts increasing amounts into the unionized form. The pH rises above pH_{max}, before dropping to the pH_{max} value. This is caused by supersaturation of the unionized form of loperamide. Immediately after this pH drop, loperamide exists in precipitated neutral form, but this is rapidly converted into the salt form.

While the pH is at pH_{max}, the rate of data collection is slowed. The system records each data point when the gradient has decayed to a value close to 0 pH/second, as shown in Figure 5. It typically takes four minutes to achieve the required stability. In figure 5 the pH drops from about 6.4 to 5.8 as KOH is consumed by converting the loperamide ion to the neutral species. After the pH has been recorded, another aliquot of KOH is added, and the next data point is recorded when the gradient has again decayed to a value close to 0 pH/second. This process continues for as long as the pH remains close to pH_{max}, until the entire salt solid has been transformed into free base solid. After the transformation is complete, the titration proceeds quickly to the specified end pH.

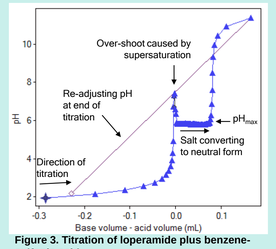

Figure 3. Titration of loperamide plus benzene-sulfonic acid.

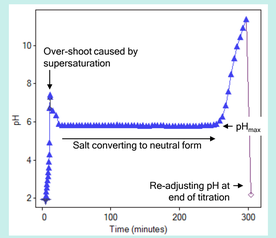

Figure 4. Data from figure 3 re-plotted to show time to convert the loperamide to neutral form.

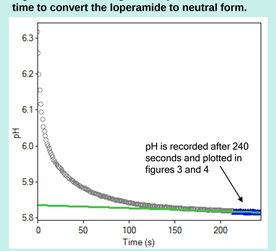

Figure 5. Drift in pH after adding aliquot of KOH.

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