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# Celebrating 40 years of the ROSS™ electrode and 50 years of $pH_{max}$

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Solubility measurement as a function of pH is critically important across several stages of pharmaceutical research: leads are first selected and optimized to identify promising clinical candidates; pre-formulation characterization is done; then the development of suitable oral drug formulations is performed. Nearly half of today's drug products are introduced in salt form. The behavior of salts as a function of pH pivots around a critical point, called '$pH_{max}$', where the conversion of salt-to-free form takes place. Some salts are unstable in water, where they spontaneously undergo this conversion, by a process of 'disproportionation'. In the characterization of salt- pH properties, the accurate measurement of pH is critical. But the importance of this is often overlooked.

Using concentrated buffers is not a good substitute for pH measurement of equilibrated saturated solutions of drugs. Yet this appears to be commonly done. The addition of drug to a buffer solution can change the final pH to values quite distant from that of the buffer. Likewise, when a low soluble free base is added to pure water, free of buffer, the drug can change the pH by several log units, making assertions about intrinsic solubility potentially useless – unless the pH is accurately measured in the final equilibated suspension.

Assessments of pH electrode junction potentials are virtually never reported in solubility studies done at the gastric pH 1.2. Most manufacturers' suggested procedures for 'calibrating' pH electrodes are suitable for quality control purposes, but usually are not sufficiently attentive to producing accurate operational pH assessment which would allow for activity corrections. [1] A pH error of 0.3 can translate to a two-fold error in solubility determination. The interpretation of solubility of surface-active/aggregation-prone molecules, especially in the pH region near the $pH_{max}$ point, can be particularly misleading.

Most of the above challenges have been discussed over the last fifty years, [1-6] but still the issues related to accurate pH measurement are not given the attention they deserve in today's pharmaceutical research. Also, salts are continuously characterized, but fundamental understanding of the multiphasic equilibrium solubility as a function of pH is unfortunately underappreciated. [3,4]

The following two papers are keystone references of note. In 1972, Kramer and Flynn [5] appear to have coined the term '$pH_{max}$', which to date centers on a key feature in the underpinnings of understanding solubility and stability of pharmaceuitcal salts. In 1981, James Ross, co-founder of Orion Research, introduced a novel type of pH sensor – the Orion ROSS™ pH combination electrode based on an iodide-iodine reference system, augmented by the signature internal reference electrode 'coil' invented by Moshe Hirshberg. [6]

This presentation will discuss and illustrate with case studies some of the issue related to inadequate uses of pH and overly simplistic interpretations of salt solubility as a function of pH. Much of what is known is barely put into practice. There remains much room for improvement in these daily tasks of pharmaceutical research.

**References**

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