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High Throughput Method to Characterize Acid-Base Properties of Insoluble Drug Candidates in Water

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Highlights:

- Fast Sequential Method is applied to study pKa(s,s) of drugs sparingly soluble in water
- Thermodynamic pKa(s,s) are obtained at different methanol/water mixtures compositions
- Two sequences provide pKa in wide solvent composition ranges
- Yasuda-Shedlovsky behavior and extrapolations are compared with empirical equations
- Exponential of pKa(s,s)+log[H2O] vs %w/w describe the behavior in the whole range

Abstract

In drug design experimental characterization of acidic groups in candidate molecules is one of the more important steps prior to the in-vivo studies. Potentiometry combined with Yasuda-Shedlovsky extrapolation is one of the more important strategy to study drug candidates with low solubility in water, although, it requires a large number of sequences to determine pK_a values at different solvent-mixture compositions to, finally, obtain the pK_a in water ($^{w}_{w}pK_a$) by extrapolation. We have recently proposed a method which requires only two sequences of additions to study the effect of organic solvent content in liquid chromatography mobile phases on the acidity of the