ADMET & DMPK 3(4) (2015) 296-297; doi: ***10.5599/admet.3.4.261***

Open Access : ISSN : 1848-7718

http://www.pub.iapchem.org/ojs/index.php/admet/index

Editorial

pK_a values in solubility determination using the Henderson-Hasselbalch equation

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Published: December 30, 2015

In this Journal we publish only high quality peer reviewed scientific papers but sometimes not all scientists can agree with all aspects of a particular paper. We wish to encourage healthy scientific debate and when appropriate it is right to publish alternative interpretations of reported experiments.

Alex Avdeef [1] and Samuel Yalkowsky [2] have independently studied the solubility and ionization properties of an investigational drug (NSC-639829). In the study conducted by Avdeef and coworkers, the pK_a value derived from Henderson-Hasselbalch (HH) equation was 4.70, which was different from the value of 3.76 as determined experimentally by the Yasuda-Shedlovsky plot using the pK_a values obtained from co-solvent UV titrations. The authors then invoked an ionization-precipitation-aggregation model by assuming the formation of a positively charged dimer to generate the theoretical solubility-pH profile. In their implementation, the pK_a was fixed at 3.76, while the S_0, and the aggregation equilibrium constant were treated as adjustable parameters. To this end, the authors obtained a reasonably good fit between the model and the experiment. The S_0 value as determined using this approach appeared to be in line with the previously reported value [2].

In this issue, Yalkowsky et al. [3] published a note to comment on the approach that Avdeef et al. [1] developed in the study of NSC-639829. In particular, they have pointed out that the pK_a of 4.70 for NSC-639829 was the correct value in the solubility determination study, and the analysis carried out by Avdeef et al. [1] was problematical. Yalkowsky et al. have highlighted that pK_a is a concentration dependent parameter, which was supported by several literature examples [3]. Apparently, Yalkowsky et al. have put forward some compelling arguments to justify their points of view in case of NSC-639829. Generally speaking, pK_a is not an absolute molecular constant because it depends very much on the medium, conditions and ionic strength of determination. For low sample concentration and/or in the presence of co-solvent, the formation of aggregate in pK_a determination is less favorable. In case of NSC-639829, the pK_a determination was accomplished by long range extrapolation from co-solvent pK_a data (22-41 % methanol-water mixtures) [1]. Again, this may introduce some uncertainty to the extrapolated pK_a value. It may be difficult to make direct comparison between the pK_a determined independently and the pK_a derived from the HH equation since the chemical/physical environments are unlikely to be the same in these two experiments.

In our opinion, Avdeef et al. [1] have developed very powerful software to analyze complex ionization-precipitation-aggregation system, which we should applaud. On the other hand, Yalkowsky et al. pointed out that effectively what the software does in the case of NSC-639829 was adding an arbitrary factor of 0.94 to bring the pK_a to 4.70. We see that these are just two different approaches to interpret the same dataset. Perhaps the aggregate formation may well be true as proposed by Avdeef et al. [1]. However, it is always difficult to prove the formation of the positively charged dimer in the equilibrium model solely based on mass balance calculation. To confirm the validity of the model, it is necessary to obtain independent structural or spectroscopic evidence.

Although this discussion centers around just one compound it is part of a wider debate regarding the applicability of the HH equation to the study of solubility where complications are likely to arise due to presence of aggregate species in solution. All the authors of these papers have made significant contributions to the field. We hope that many scientists with an interest in solubility and ionization will read both papers and learn from the differing views of these eminent researchers.

References

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