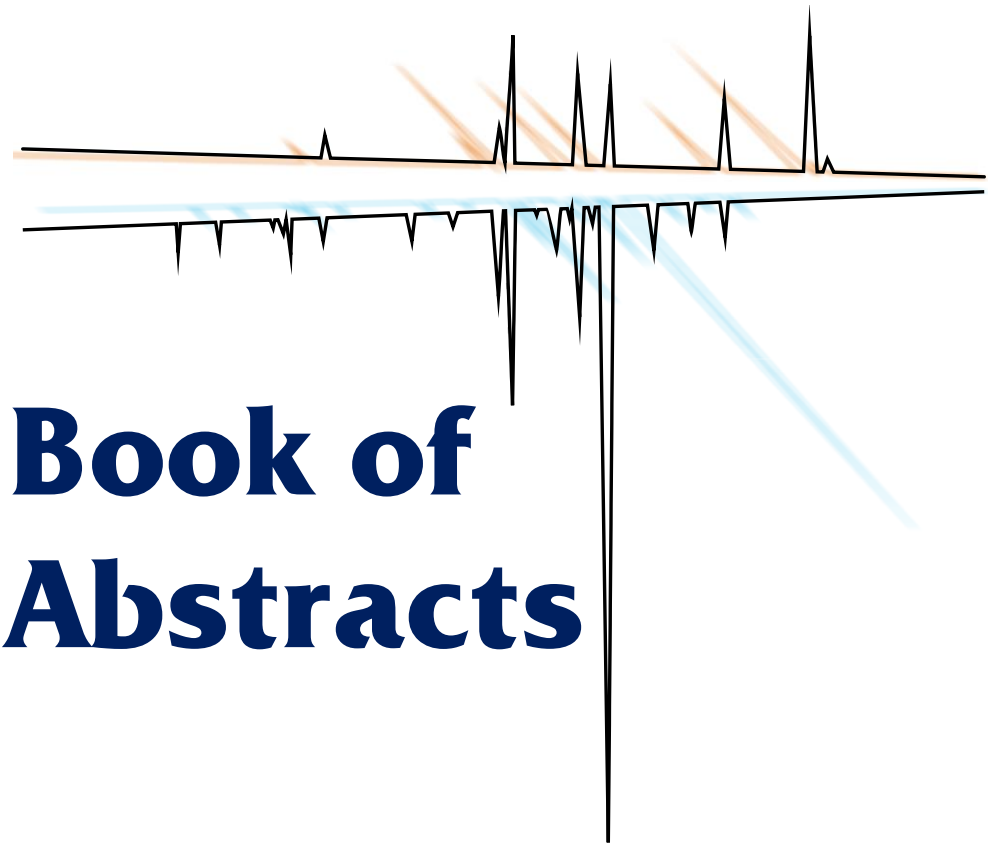
8th IAPC Meeting

Eighth World Conference on Physico-Chemical Methods in Drug Discovery

&

Fifth World Conference on ADMET and DMPK



Book of Abstracts

Split, Croatia, September 9-11, 2019

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Zoran Mandić

Editor
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O 16

Desipramine solubility studies: enhanced solubility due to drug-buffer aggregates

Olivera S. Marković, Miloš P. Pešić[1], Ankita V. Shah[2,3], Abu T.M. Serajuddin[2], Alex Avdeef[4], Tatjana Ž. Verbić[1,✉]

Department of Chemistry, IChTM, University of Belgrade, Belgrade, Serbia
[1]University of Belgrade – Faculty of Chemistry, Belgrade, Serbia
[2]St. John's University, College of Pharmacy and Health Sciences, NY, USA
[3]Current address: Freund-Vector Corporation, IA, USA
[4]in-ADME Research, New York, USA
✉tatjanad@chem.bg.ac.rs

Optimal experimental design to measure the aqueous equilibrium solubility of an ionizable substance requires a number of critical considerations. The aqueous medium to which the substance is added usually contains a buffer to help control the pH.

The solution behavior of desipramine hydrochloride (DsHCl) in phosphate-buffered and unbuffered solutions is evidently complicated and only tentatively understood. The computer program *p*DISOL-X was used to design the structured pH-ramp shake flask experiments (pH-RSF method), to process the data, and to refine the equilibrium constants. Specifically, solubility was measured: a) using *state-of-the-art* experimental design, as recommended in a recently published *white paper* on solubility [1], b) performing solubility titrations in two directions, pH 11.6→1.3 as well as 1.3→11.6, c) using both DsHCl and Ds (free base), as starting solids, d) performing titrations in chloride-containing media, without any phosphate, e) performing the converse measurements (phosphate-containing, chloride-free media), f) isolating solids at critical log *S*-pH points and performing solid state characterizations using elemental, thermogravimetric, differential scanning calorimetric, and powder X-ray diffraction analyses. Concentration was measured using HPLC with UV/VIS detection.

Under the assay conditions, only the phosphate free solutions showed some supersaturation near pH_{max} 8.0. In phosphate-containing solutions, pH_{max} was indicated at higher pH (8.8–9.6). Oils mixed with solids were observed to form in alkaline solutions (pH>11). Notably, soluble drug-phosphate *complexes* appeared to form below pH 3.9 and above pH_{max} in saturated phosphate‑containing saline solutions. This was indicated by the systematic pH shift to higher values in the log *S*-pH curve in alkaline solution than expected from the Henderson-Hasselbalch equation. For pH<3.9, saturated phosphate-containing saline solutions exhibited elevated solubility, with drug-*hydrochloride* as the sole precipitate. Salt solubility products, intrinsic solubility, and complexation constants, which rationalized the data, were determined [2].

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