

**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

8th IAPC Meeting

*Eighth World Conference on Physico-Chemical Methods in Drug Discovery
&*

*Fifth World Conference on ADMET and DMPK
Split, Croatia, September 9-11, 2019*

Book of Abstracts

Published by

International Association of Physical Chemists

E-mail: office@iapchem.org, URL: <http://www.iapchem.org>

For Publisher

Zoran Mandić

Editor

Zoran Mandić

Design, Page Making and Computer Layout

Aleksandar Dekanski

On Line version only

The Scientific and Organizing Committee:

Alex Avdeef, In-ADME Research, USA

Christel Bergström, Uppsala University, Sweden

Biserka Cetina-Čižmek, PLIVA, Croatia

Zoran Mandić, University of Zagreb, Croatia - conference chair

Abu Serajuddin, St. John's University, USA

Kiyohiko Sugano, Ritsumeikan University, Japan

Kin Tam, University of Macau, Macau - conference co-chair

Klara Valko, Bio-Mimetic Chromatography, UK

Tatjana Verbić, University of Belgrade, Serbia

Organization of IAPC-8 Meeting is supported by



Sponsors and Exhibitors



P 16

pH-Dependent solubility profiles of imipramine and amitriptyline hydrochlorides

Olivera S. Marković, Miloš P. Pešić¹, Alex Avdeef², Tatjana Ž. Verbić¹,✉

Department of Chemistry, IChTM, University of Belgrade, Belgrade, Serbia

¹University of Belgrade – Faculty of Chemistry, Belgrade, Serbia

²in-ADME Research, New York, USA

✉ tatjanad@chem.bg.ac.rs

Amphiphilic tricyclic bases are surface-active, sparingly-soluble drugs, which can exhibit complicated aqueous solution chemistry. New pH-Ramp Shake-Flask method was previously applied to desipramine hydrochloride solubility studies and described in the literature [1]. Solubility was measured using *state-of-the-art* experimental design, recommended in the *white paper* on equilibrium solubility measurements [2]. The aim of this study was to examine solubility-pH behavior of desipramine structural analogues: imipramine and amitriptyline hydrochlorides (**Figure 1**). Imipramine and amitriptyline are tricyclic antidepressants, which are used in the treatment of mental illnesses. pH-Ramp Shake-Flask method was applied.

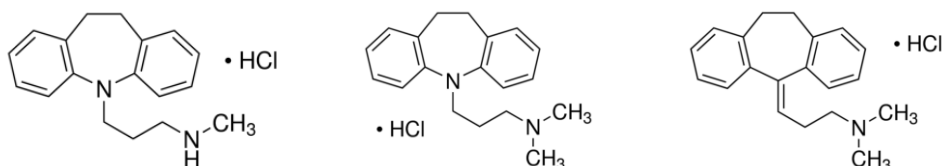


Figure 1. Structures of desipramine, imipramine, and amitriptyline hydrochlorides, respectively.

Appearance of aggregates (trimer, around pH 4 in imipramine case), which lead to slow sedimentation, and oil forms make solubility determination extremely challenging. Oils which are more soluble than crystalline forms are formed in alkaline solutions (above pH 7.8 in imipramine case). Sometimes in such cases, pH adjustment in that pH region can be unpredictable. Furthermore, oil sticks to electrode making pH measurement difficult, especially in amitriptyline case. Concentration was measured using HPLC with UV/Vis detection. Different techniques were used for solid phase characterization. Solid phase characterization is particularly important in complicated systems like this.

Acknowledgement: Ministry of Education, Science and Technological Development of Serbia supported this work (Grant No. 172008 and 172035).

References:

1. O.S. Marković, M.P. Pešić, A.V. Shah, A.T.M. Serajuddin, T.Ž. Verbić, A. Avdeef, Solubility-pH profile of desipramine hydrochloride in saline phosphate buffer: Enhanced solubility due to drug-buffer aggregates, *Eur. J. Pharm. Sci.* **133** (2019) 264–274.
2. A. Avdeef, E. Fuguet, A. Llinas, C. Rafols, E. Bosch, G. Volgyi, T. Verbić, E. Boldyreva, K. Takacs-Novak, Equilibrium solubility measurement of ionizable drugs consensus recommendations for improving data quality, *ADMET&DMPK* **4** (2016) 117–178.