International Association of Physical Chemists

10th IAPC Meeting, 4-6 September 2023, BELGRADE, Serbia

Physico Chemical Methods Drug Discovery & Development
(www.iapchem.org)

Special Session on Solubility of Pharmaceuticals

"Solubility of Multi-Component Solids (Salts and Cocrystals)"

Session co-chairs: **Kiyohiko Sugano** (Ritsumeikan University, Japan) and **Alex Avdeef** (*in-ADME* Research, USA)

The IAPC-10 conference takes place in the ancient city of Belgrade at the confluence of the Sava and Danube rivers. Its history dates to at least 7000 BC. The first farmers to settle in the region are associated with the Neolithic people, representing one of the earliest settlements by continuous habitation and some of the largest in prehistoric Europe. After 279 BC Celts conquered the city. It was settled by the Slavs in the 520s. Since 1521 it frequently passed from Ottoman to Habsburg rule, which saw the destruction of most of the city during the Austro-Ottoman wars. It was the cite of battles in over a hundred wars and razed to the ground nearly fifty times. Belgrade became the capital of Serbia in 1841. After 1918 it became the capital of Yugoslavia until the dissolution of the country in 2006. It remains now the capital of Serbia.

Since 2009, the *International Association of Physical Chemists* (**IAPC**) conferences have included special sessions covering solubility measurement and interpretation.

- **IAPC-4** (Red Island, Croatia, 21-24 September 2015): *"Thermodynamic Solubility Measurement of Practically Insoluble Ionizable Drugs – Case Studies & Suggested Method Improvements"* session resulted in a publication drawing on expert consensus opinions from researchers in six countries (Hungary, Russia, Serbia, Spain, Sweden, United States) [https://doi.org/10.5599/admet.4.2.292]. The commentary reached *2509 reads* and *74 citations* in ResearchGate (*92* in Google Scholar) by 8 Feb 2023.
- **IAPC-6** (Zagreb, Croatia, 4-7 September 2017): *"Pharmaceutical Cocrystals - Physicochemical Properties and Formulations"* special session included cutting-edge presentations from internationally-recognized experts in cocrystal solubility-pH measurement. Several publications on the topic emerged out of the meeting.
- **IAPC-8** (Split, Croatia, 9-11 September 2019): *"State-of-the-Art Solubility Methods in Drug Development"* session continued the symposia on the topic of solubility of pharmaceuticals. One of the associated session papers [http://dx.doi.org/10.5599/admet.686] reached *2845 reads* and *38 citations* in ResearchGate by 8 Feb 2023.
- **IAPC-10** (Belgrade, Serbia, 4-6 September 2023): *"Solubility of Multi-Component Solids (Salts and Cocrystals)"* session, co-chaired by Kiyohiko Sugano (Ritsumeikan University) and Alex Avdeef (*in-ADME* Research), will strive to carry on the symposia on the topic of solubility of pharmaceuticals.

BACKGROUND: SALTS AND COCRYSTALS

Poorly-soluble ionizable drugs ordinarily show low intestinal absorption. For orally administered drugs, the extent of intestinal absorption depends on the rate of release of the active pharmaceutical ingredient (API) from the solid form, which depends on the solubility of the API. [1]

To increase absorption, such drugs are often formulated as salts (charged API + counterion).[2-8] A newly developing strategy is based on cocrystal formulations (uncharged API + coformer).[9-13] A better understanding of the water solubility of salts and cocrystals is important for drug discovery and development. Salt and cocrystal forms can release the API in a supersaturated state, which can enhance absorption. However, this state may be short-lived. In the case of salts, disproportionation can release the uncharged form of the API, greatly reducing the concentration of the API in solution. The same can happened with cocrystals, as the supersaturated uncharged API may precipitate.

COCRYSTALS ENHANCEMENT OF SOLUBILITY

Formulation strategies based on using cocrystals have been developed to increase intestinal absorption.[9-11] Cocrystals are materials composed of two or more different *uncharged* molecules (API + coformer) within the same crystal lattice that are associated by nonionic and noncovalent bonds. The altered solid-state properties in cocrystals are generally expected to elevate the drug concentration in a similar way that drug salts do, as the drug is released in a dissolution process. The elevated concentration of the drug could lead to increased oral absorption of the drug. The analyses of solubility of salts and cocrystals are similar since both are multi-component solids. Drug salts are characterized by a solubility product, K_{sp}^{SALT}= [API][counterion], where the API and counterion are charged species. Cocrystals are similarly characterized by an equilibrium solubility product, K_{sp}^{CC} = [API][coformer], but in contrast to salts, both the drug and the coformer are uncharged in the cocrystal. A method to predict K_{sp}^{CC} and the solubility enhancement of cocrystals, using an approach based on measured drug and coformer intrinsic solubility (S_0^{API}, S_0^{COF}), combined with *in silico* H-bond descriptors, has been recently described.[12] The latter publications arose out of the IAPC-6 special session on cocrystal solubility.

SALT ENHANCEMENT OF SOLUBILITY

Salt disproportionation in aqueous solution affects the stability of the suspension formulations for preclinical animal studies. The in-depth understanding of disproportionation is important to understanding the dissolution of a drug in biorelevant low buffer media.

The properties of drug salts and cocrystals continue to be better understood, and traditional notions about salts or cocrystals require updating from time to time, as more in-depth studies are reported. The speakers at the IAPC-10 special session on the solubility of multicomponent solids (salts and cocrystals) will address this topic.

When a pharmaceutical salt containing an ionizable API is added to pure water to form a saturated solution, the solubility of the API is commonly called 'S_w'. But this is somewhat under-informative.

TWO TYPES OF SALTS – DEFINITION OF TERMS

NONDISPROPORTIONATING SALT (μ stands for 'microclimate')

The 2-phase system (1 solid + 1 liquid) represents a stable saturated solution, where the *excess solid* in the salt suspension in pure water is the original salt form. The *pH* and solubility can be labeled $\boldsymbol{pH_\mu}$ and $\boldsymbol{S_\mu}$, with **μ** signifying the 'microclimate' environment expected at the solid-liquid interface of dissolving salt particles.

The value of *pH* is not dependent on the amount of added salt.[2,8] For a weak-base API, generally, $\boldsymbol{pH_\mu} < \boldsymbol{pH_{max}}$. The $\boldsymbol{pH_\mu}$ can be calculated given the measured $\boldsymbol{S_\mu}$ and the supplied pK_a values of the API and the counterion (if ionizable). Since the suspension does not contain the API in the free form, the intrinsic solubility, $\boldsymbol{S_0}$, *cannot* be determined from the one-pH measurement in water.

SPONTANEOUSLY DISPROPORTIONATING SALT (δ stands for 'disproportionating') [3,6,7]

The 3-phase state (2 solids + 1 liquid) may be called a '**eutectic mixture**' (EM) of two solids (original salt plus the uncharged API form). The *pH* of the EM is not a discrete value – rather, it spans a range of *pH*, bounded at one end by the traditional $\boldsymbol{pH_{max}}$ and at the other end by $\boldsymbol{pH_{min}}$, a recently described designation.[6,7] The solubility of the EM suspension formed is called $\boldsymbol{S_\delta}$; the *pH* of the δ-type salt suspension is termed $\boldsymbol{pH_\delta}$. In the case of a weak-base API, $\boldsymbol{pH_{max}} < \boldsymbol{pH_\delta} < \boldsymbol{pH_{min}}$. The exact apportionment *depends on the amount of added drug salt*. Since the EM suspension contains two excess solids, it is possible to calculate the value of the intrinsic solubility, $\boldsymbol{S_0}$, and the $\boldsymbol{pH_\delta}$, given the measured $\boldsymbol{S_\delta}$ and the supplied pK_a values of the API and the counterion (if ionizable). The calculated $\boldsymbol{S_0}$ value may be slightly overestimated in some cases, due to residual supersaturation during the $\boldsymbol{S_\delta}$ measurement.

$\boldsymbol{pH_{max}}$ is the *pH* at the maximum solubility of the EM suspension, marked by a discontinuity in the log *S*-*pH* curve; $\boldsymbol{pH_{min}}$ is pH at the minimum solubility of the EM suspension, marked, *e.g.,* by a discontinuity in the *pH* vs. volume of NaOH titration curve.

REFERENCES

1. Hörter D, Dressman JB. Influence of physicochemical properties on dissolution of drugs in the gastrointestinal tract. *Adv. Drug Deliv. Rev.* 25 (**1997**) 3-14.

2. Serajuddin ATM. Salt formation to improve drug solubility. *Adv Drug Delivery Rev* 59 (**2007**) 603-616.

3. Merritt JM, Viswanath SK, Stephenson GA. Implementing quality by design in pharmaceutical salt selection: a modeling approach to understanding disproportionation. *Pharm Res* 30 (**2013**) 203-217.

4. Hsieh YL, Merritt JM, Yu W, Taylor LS. Salt stability–the effect of pH_{max} on salt to free base conversion. *Pharm Res* 32 (**2015**) 3110-3118.

5. Bharate SS. Recent developments in pharmaceutical salts: FDA approvals from 2015 to 2019. *Drug Discov Today* (**2020**), doi: https://doi.org/10.1016/j.drudis.2020.11.016.

6. Avdeef, A. Disproportionation of Pharmaceutical Salts: pH_{max} and Phase-Solubility/pH Variance. *Mol. Pharmaceutics* 18 (**2021**) 2724-2743. https://pubs.acs.org/doi/10.1021/acs.molpharmaceut.1c00258.

7. Avdeef A, Sugano K. Salt solubility and disproportionation - uses and limitations of equations for pHmax and the in-silico prediction of pHmax. *J Pharm Sci* 111 (**2022**) 225-246. https://doi.org/10.1016/j.xphs.2021.11.017.

8. Uekusa T, Avdeef A, Sugano K. Is equilibrium slurry pH a good surrogate for solid surface pH during drug dissolution? *Eur J Pharm. Sci* 168 (**2022**) 106037. https://doi.org/10.1016/j.ejps.2021.106037.

9. Childs SL, Rodríguez-Hornedo N, Reddy LS, Jayasankar A, Maheshwari C, McCausland L, Shipplett R, Stahly BC. Screening strategies based on solubility and solution composition generate pharmaceutically acceptable cocrystals of carbamazepine. *Cryst. Eng. Comm*. 10 (**2008**) 856-864.

10. Brittain, H.G. Cocrystal systems of pharmaceutical interest: 2011. *Cryst. Growth Des*. 12, (**2012**) 5823-5832.

11. Kuminek, G., Rodríguez-Hornedo, N., Siedler, S., Rocha, H.V.A., Cuffini, S.L., Cardoso, S.B. How cocrystals of weakly basic drugs and acidic coformers might modulate solubility and stability. *Chem. Commun*. 52 (**2016**) 5832-2835.

12. Avdeef A. Cocrystal Solubility Product Prediction Using an in combo Model and Simulations to Improve Design of Experiments. *Pharm. Res*. 35 (**2018**) Article number: 40. https://doi.org/10.1007/s11095-018-2343-3.

13. Guidetti, M., Hilfiker, R., Kuentz, M., Bauer-Brandl, A., Blatter, F. (2022). Exploring the cocrystal landscape of posaconazole by combining high-throughput screening experimentation with computational chemistry. *Crystal Growth & Design* Article ASAP. https://doi.org/10.1021/acs.cgd.2c01072.