In silico approaches to drug stability and solubility

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Introduction

- One of the major concerns in modern drug discovery and development is chemical and physical stability of small molecule pharmaceuticals.

- Chemical stability is crucial for compounds at all stages of pharmaceutical R&D, from early drug discovery to formulation of liquid or solid dosage forms.

- Physical stability is typically related to stability of the solid form and can be described by such properties as melting point, heat and free energy of fusion and energies of sublimation.

I. Chemical Stability

- There are multiple degradation mechanisms of pharmaceuticals, including oxidation, hydrolysis, photochemical and reaction with reactive excipient impurities.

- In this study we focus on electron withdrawing oxidative chemical stability.

Chemical Stability

- Oxidation is defined broadly as the loss of electron(s) from a molecule.
- Drug degradation due to the oxidative instability is a significant concern of formulation studies:

K.C.Waterman *et al*, *Pharmaceutical Development and Technology*, 7, 1-32 (2002).

- Molecular degradation is no less important at the early stages of drug discovery. It gives rise to misleading SAR and misinterpretation of biological experiments
- As such, it is necessary to develop tools that help to recognize and predict the electron-transfer induced oxidative instability of small molecules. Both statistical and quantum-mechanical approaches were utilized in this study .

II. Physical stability of Pharmaceuticals

- 80% of all drug substances are formulated in solid-dosage forms.
- Pharmaceutical physical stability is typically related to stability of commercial form throughout the shelf life. The current computational methods for that are reviewed at:

  Abramov Y.A. Current Computational Approaches to Support Solid Form Selection. *OPRD* 2013, 17, 472-485.

- Here we focus on three topics related to the physical stability:

  1) Virtual hydrate screening

  2) Computational support of solid form selection

  2) Drug poor solubility and crystal packing effects

Virtual hydrate screening and coformer selection for improved relative humidity stability

Drug formulations of anhydrous solid forms are generally preferred over hydrated forms. This is due to the risks of low exposure and unacceptable physical and chemical stability in comparison with anhydrous formulations. The purpose of the current study was to determine which descriptors can be most efficiently applied to virtual screening in order to provide answers to the following questions:

- what is the propensity to form a solid state hydrate of a pharmaceutical compound
- in regards to cocrystalline formulation, which coformer would provide for the highest stability with respect to relative humidity (RH) conditions?

Abramov, Y.A. *CrystEngComm* **2015**, DOI: 10.1039/c4ce02523g
Abramov, Y.A., Loschen, C, Klamt, A. *J. Pharm. Sci.*, 2012, **101**, 3687-3697.

Virtual hydrate screening

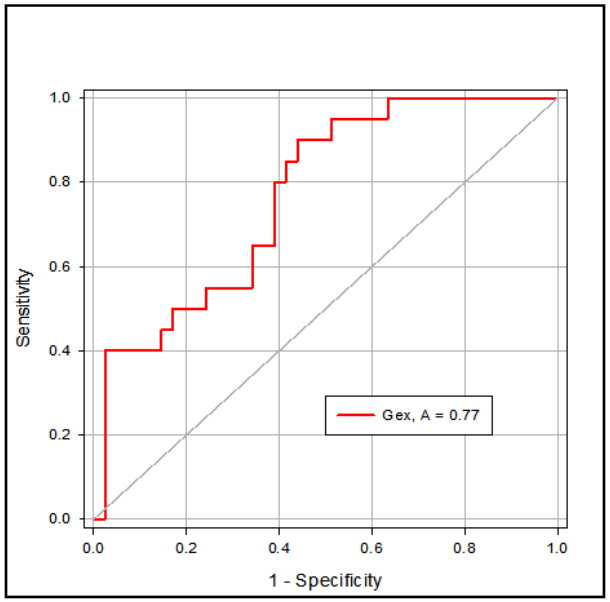
Dataset: 41 observations of hydration were taken from different literature sources of hydrated APIs. In addition 20 cases of compounds not forming solid hydrates.

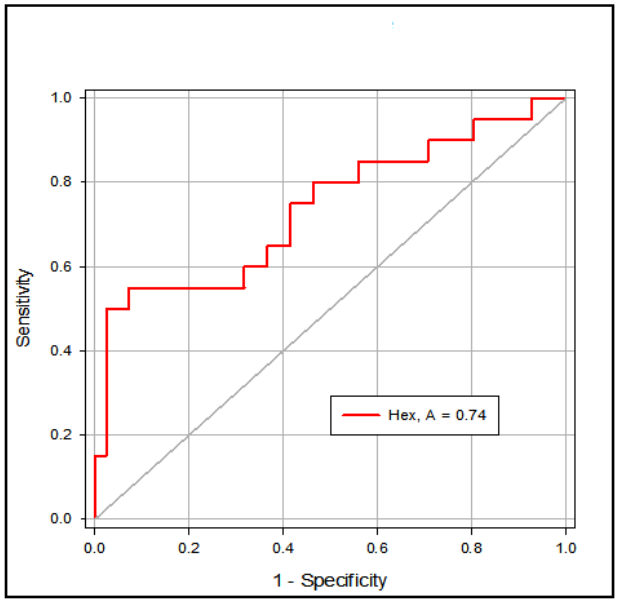
Descriptor	Positive direction	AUC
G_{ex}	High	0.77
H_{ex}	High	0.74
clogP	High	0.72
RDA	High	<0.5
DDA	Low	<0.50
SDA	Low	0.57
TPSA	Low	0.57

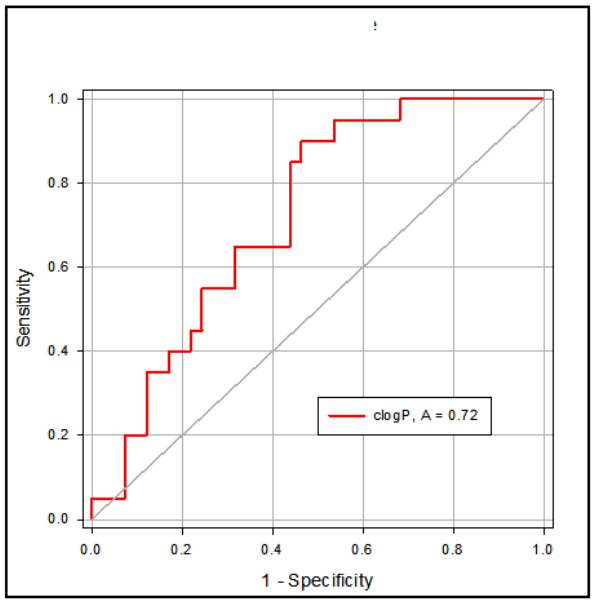
COSMO-RS descriptors:

$$G_{ex} = G_{AB} - x_m\, G_{pure,A} - x_n\, G_{pure,B}$$
$$H_{ex} = H_{AB} - x_m\, H_{pure,A} - x_n\, H_{pure,B}$$

Virtual hydrate screening: ROC curves

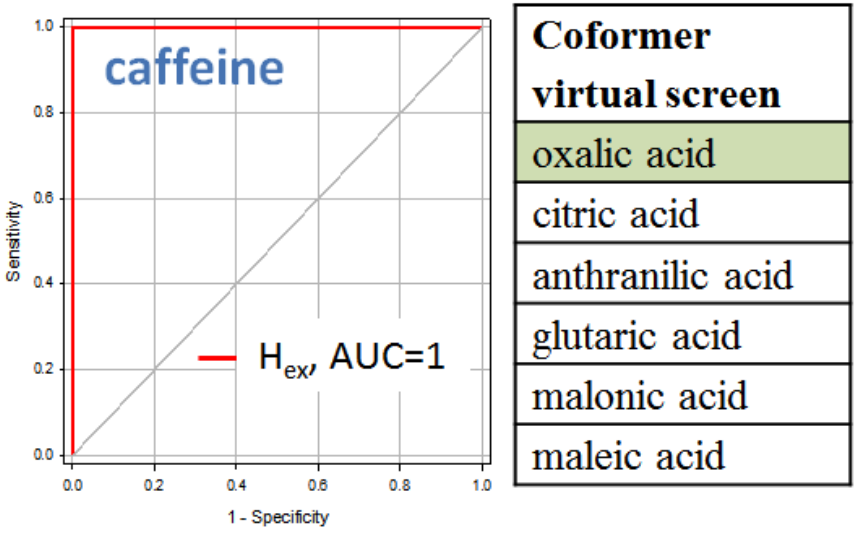




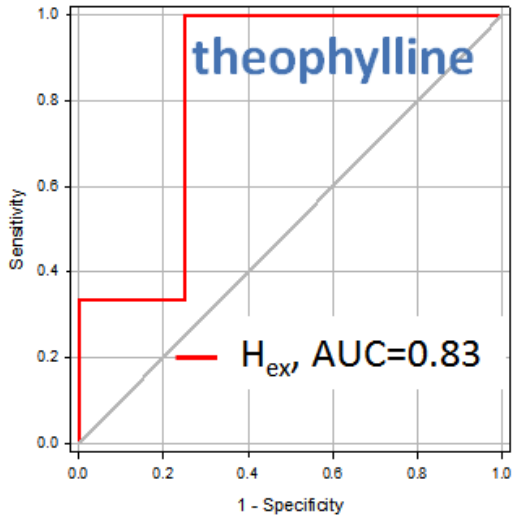


In silico coformer screening for an improved stability at high RH

It has been shown previously that cocrystallization of APIs that form both hydrate and anhydrous solid forms (such as carbamazepine, caffeine and theophylline) may lead to stabilization against hydrate formation. In this study we tested virtual screening models that are based on API-coformer miscibility (interaction) in a supercooled liquid state as measured by COSMO-RS excess enthalpy H_{ex},[1] as well as on experimental coformer aqueous solubility values, S_{cof}, and water-cocrystal miscibility as measured by G_{ex}.



Coformer virtual screen
oxalic acid
citric acid
anthranilic acid
glutaric acid
malonic acid
maleic acid

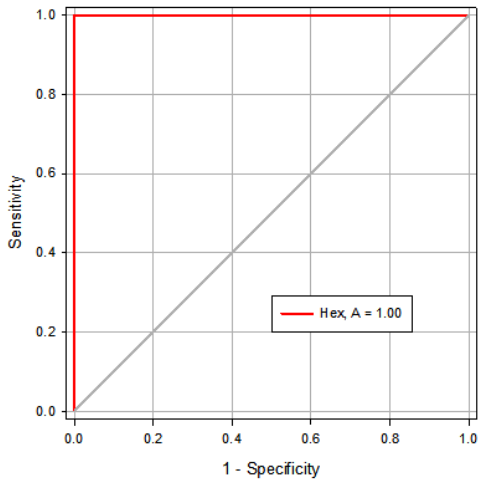


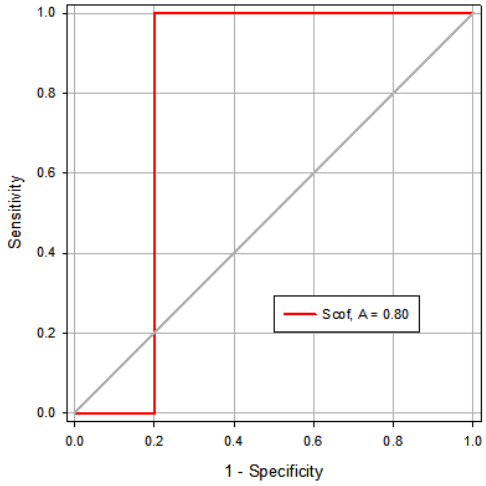
Coformer virtual screen
oxalic acid
citric acid
diflunisal
diclofenac
malonic acid
glutaric acid
maleic acid

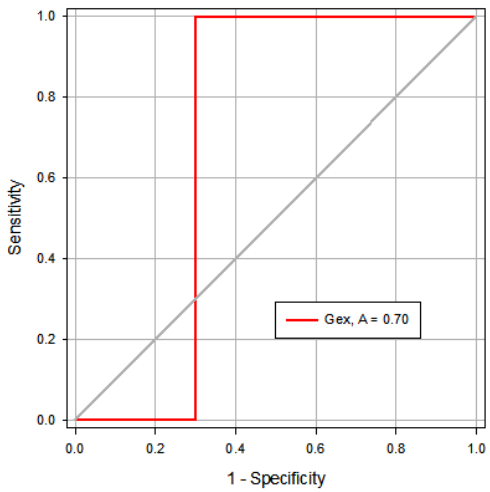
1. Y. A. Abramov, C. Loschen and A. Klamt, *J. Pharm. Sci.*, 2012, **101**, 3687-3697.

In silico coformer screening for an improved stability at high RH

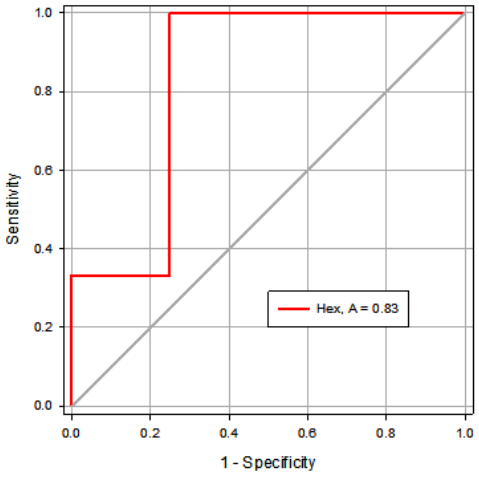
Caffeine

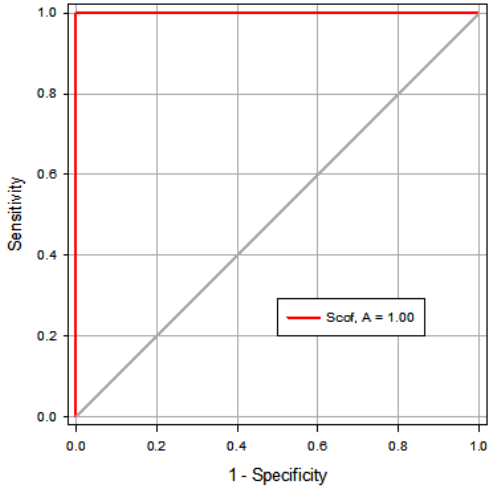


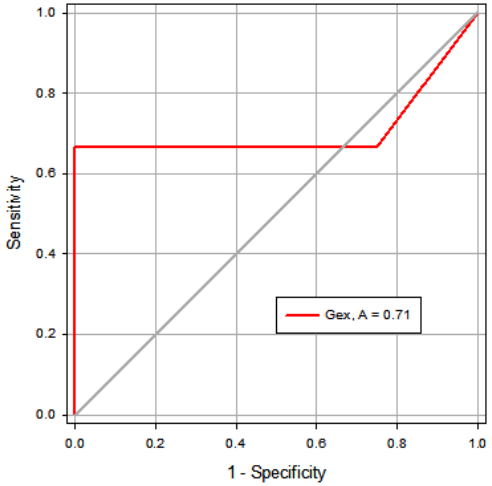




Theophylline







Computational assessment of a likelihood of a missed stable form

The importance of thermodynamically stable form selection in the pharmaceutical industry can be illustrated by well-known examples of polymorph-induced impacts on marketed drugs – Norvir® (ritonavir) and Neupro® (rotigotine patches). In the first case, Abbott Laboratories had to stop sales of Norvir in 1998 due to a failure in a dissolution test, which was caused by the precipitation of a more stable and less soluble form II of the compound.

In the second example, undesirable crystallization of rotigotine was found in the patches that were used to administer the drug. These crystals formed as a result of a previously unknown stable polymorph of rotigotine, causing UCB to suspend the marketing of this drug in the US.

Bauer, J. et al. *J. Pharm. Res*. **2001**, 18, 859−866.
Kempf, D. J. et al. *Proc. Natl. Acad. Sci. U.S.A.* **1995**, 92 , 2484−2488.
Rascol, O.; Perez-Lloret, S. *Expert Opin. Pharmacother.* **2009**, 10, 677−691.

Computational assessment of a likelihood of a missed stable form

State-of-the art computational approaches were developed to guide polymorph screening and support the solid form nomination:

- Crystal Structure Prediction (CSP)
- H-bonding propensity analysis
- Rational solvent selection to guide polymorph screening experiments

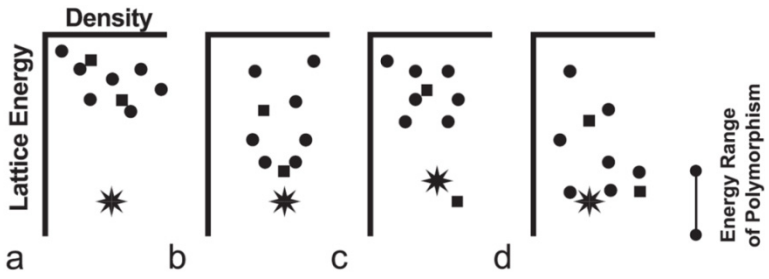
A common current limitation of the first two methods is inability to account for an enantiotropic relationship between the polymorphs near or below ambient temperature. Therefore in order to mitigate limitations it was recommended to support solid form selection based on a combination of all the methods.

Abramov, Y.A. *OPRD*, 2013, 17, 472-485

Crystal structure prediction: limitations

- **Potential energy**
- **Temperature effect**
- **Kinetic affects**
- **Molecular flexibility**
- **Number of molecules in asymmetric unit**

Due to the multiple limitations, perhaps only crystal energy landscape, in which the observed form is separated from all other structures (Figure 1a) or from a global minimum in energy (Figure 1c) by a substantial energy gap (~4-5 kJ/mol), may provide a reliable insight into the risk assessment of the solid form selection.



Day, G. M., *Crystallography Reviews* **2011**, *17* (1), 3-52.

H-bonding propensity analysis to support solid form selection

An alternative simplified approach to the classification of polymorph stability is based on selected dominant interactions analyses. H-bonds are the strongest and most specific (directional) interactions, they typically play a dominant role in the crystallization and stability of pharmaceutical solids.

- **Knowledge-Based Model**

  A probabilistic approach to analyses of organic crystals stability was developed based on statistical analysis of hydrogen bonds in the CSD.

  Galek, P. T. A. et al, *Acta Crystallographica Section B: Structural Science* **2007**, *63* (5), 768-782.

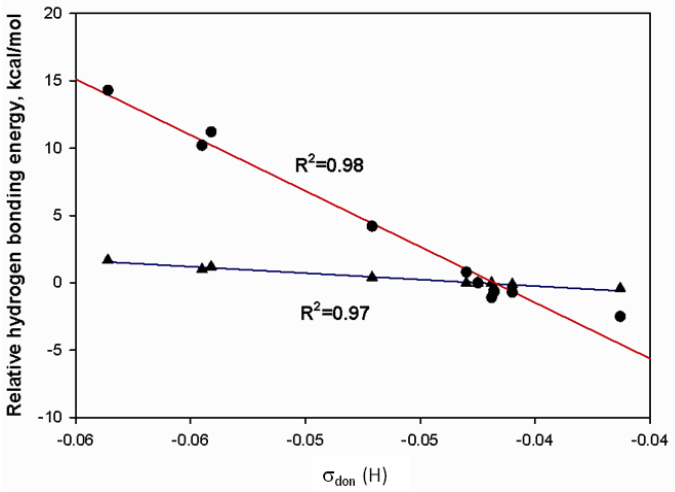
- **Theoretical approach**

  Is based on σ H-bonding screening charges (COSMO-RS).

  Abramov, Y.A. *OPRD*, 2013, 17, 472-485;

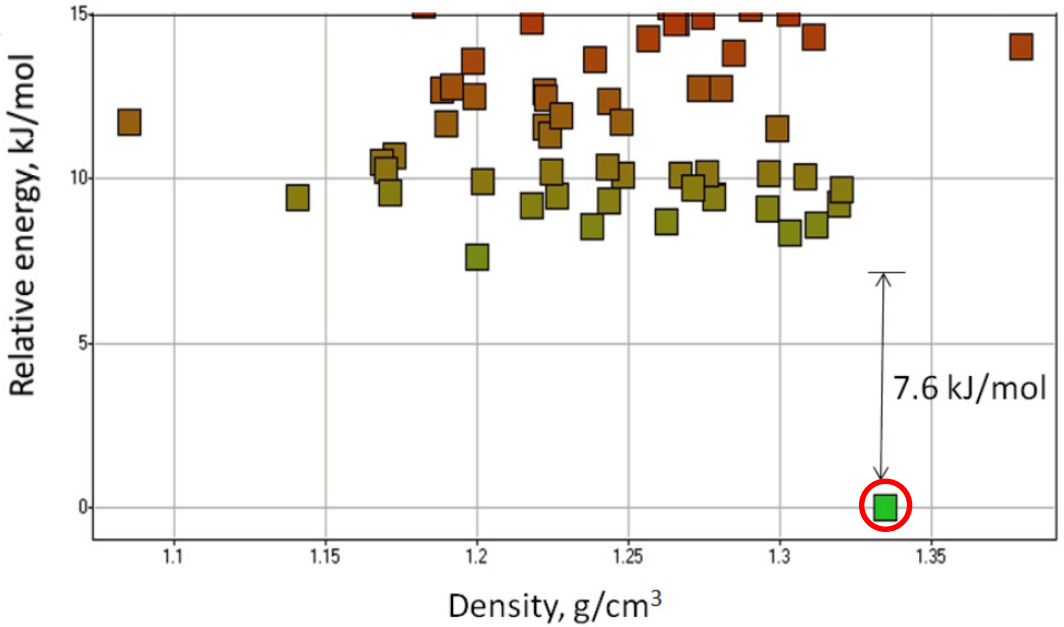
  Klamt, A. et al.*Phys. Chem. Chem. Phys*. 2012, 14, 955−963.

  H-bonding interactions of substituted phenols with formaldehyde (blue line) and acetate anion (red line) acceptor probes are described by σ donor charges.

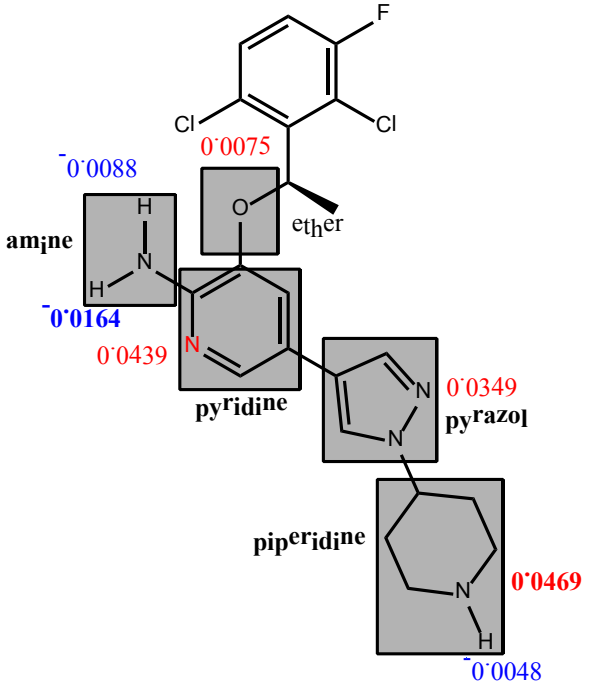


Computational support of Xalcory® (crizotinib) solid form selection

CSP



H-bonding analysis



Donor	Acceptor	π	Bond formed
amine	pyridine	0.750	X
amine	piperidine	0.673	X
amine	pyrazole	0.532	-
piperidine	pyrazole	0.153	-
piperidine	ether	0.023	X

Based on these considerations, the likelihood of finding a more stable polymorph is low.

Abramov, Y.A. *OPRD*, **2013**, 17, 472-485

Drug poor solubility issue

"Despite significant efforts to "design in" acceptable developability properties (including aqueous solubility) during lead optimization, approximately 40% of currently marketed compounds and most current drug development candidates remain poorly water-soluble" [1].

Therefore in order to guide medicinal chemistry lead optimization we need to find the way to understand whether solubility is limited by solid state or molecular property contribution.

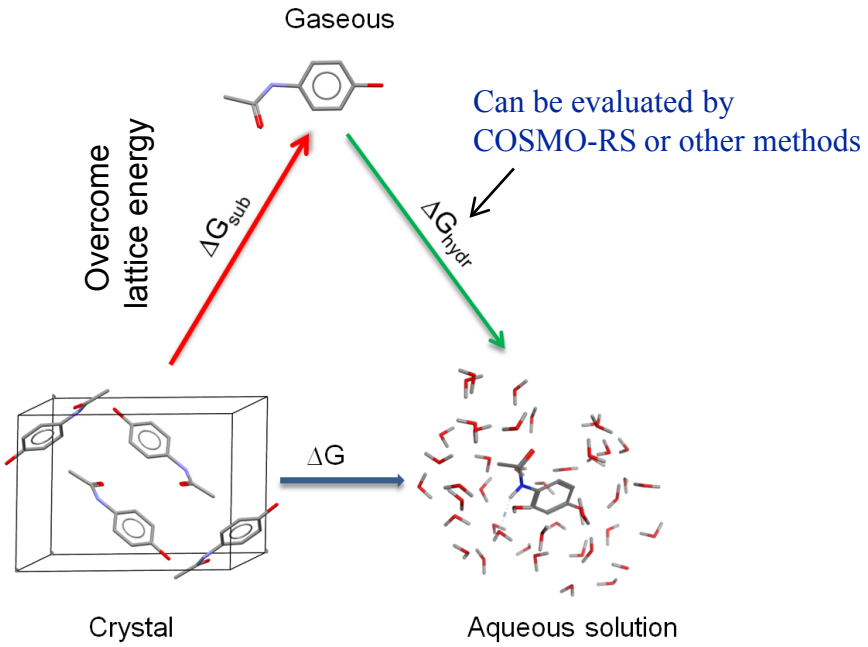
1. Williams H.D. et al. Pharmacol Rev 65:315–499, 2013.

Drug Solubility and crystal packing effects

Sublimation cycle[1]

$$\log S_0 = -(\Delta G_{sub} + \Delta G_{hydr})/2.3RT$$

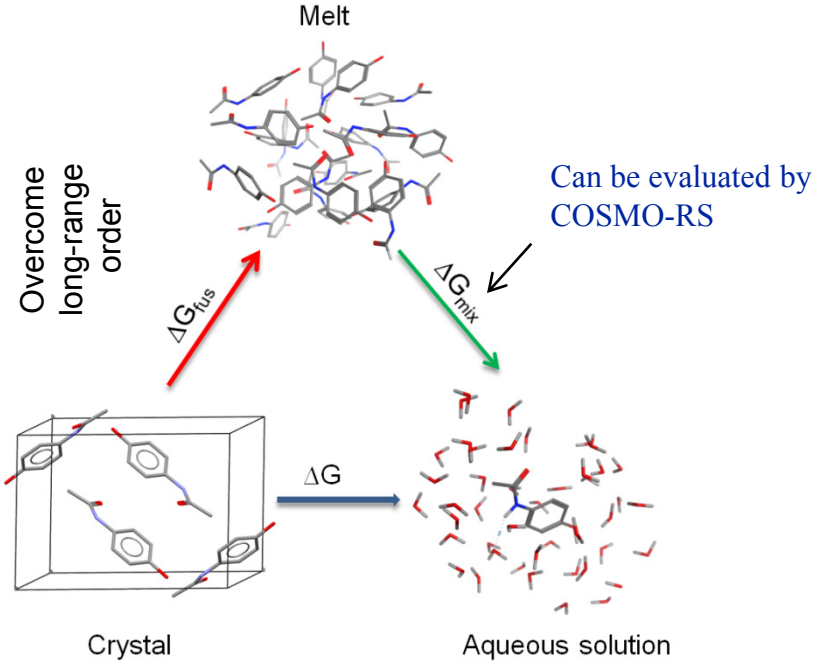
Molecule in gas phase



Melting Cycle[2]

$$\log S_0 = -(\Delta G_{fus} + \Delta G_{mix})/2.3RT$$

Molecule in a supercooled liquid



1.Palmer, D. S.; Llinas, A., Morao, I.; Day, G. M.; Goodman, J. M.; Glen, R. C.; Mitchell, J.B.O. 2008. Mol. Pharm. 5, 266-279 .

2. Abramov, Y.A.; Pencheva K. "Thermodynamics and Relative Solubility Prediction of Polymorphic Systems", In *Chemical Engineering in the Pharmaceutical Industry: from R&D to Manufacturing*; am Ende, D.J., Ed.; Wiley: New York, 2010, 477-49

Drug Solubility and crystal packing effects

Solid state contribution to solubility in a simple way was introduced by Yalkowsky and coworkers *via* general solubility equation (GSE):[1]

$$\log S_0 = 0.5 - 0.01(T_m - 25) - \log P$$

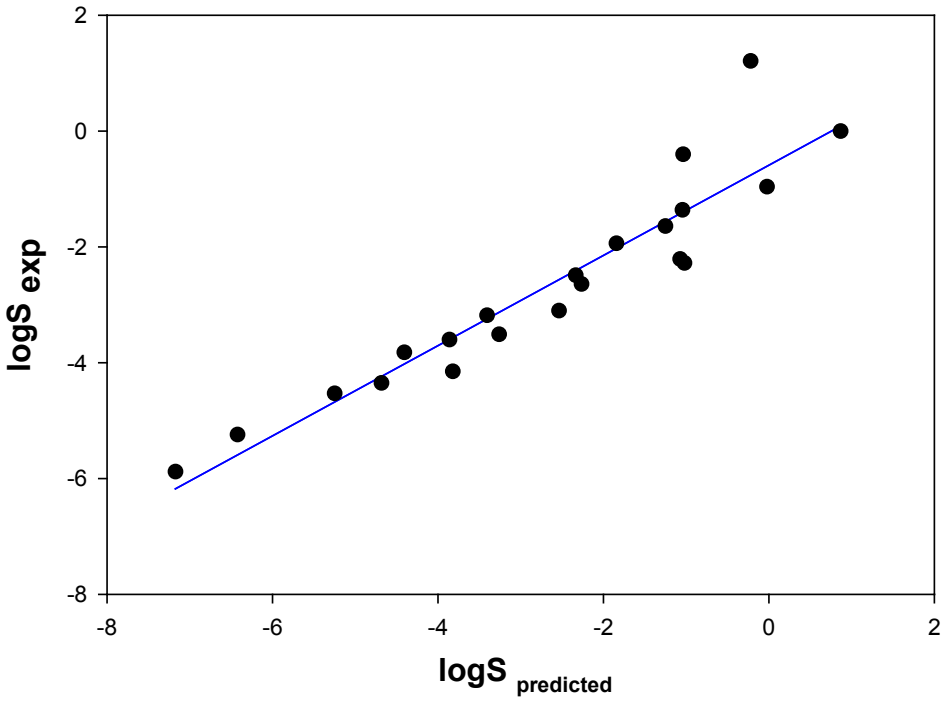
However, the true crystal stability is not measured only by melting point,[2] as well as octanol-water partition coefficient is not the exact measure of molecular hydration energy.

So we need to go back to basics to better describe crystal packing *vs* molecular contribution to poor solubility of drug-like molecules.

[1]Jain, N; Yalkowsky, S.H. J. Pharm Sci, **2001**, *90*, 234.
[2]Abramov, Y.A.; Pencheva K. "Thermodynamics and Relative Solubility Prediction of Polymorphic Systems", In *Chemical Engineering in the Pharmaceutical Industry: from R&D to Manufacturing*; am Ende, D.J., Ed.; Wiley: New York, **2010**, 477.

Drug Solubility and crystal packing effects: Proof of Concepts

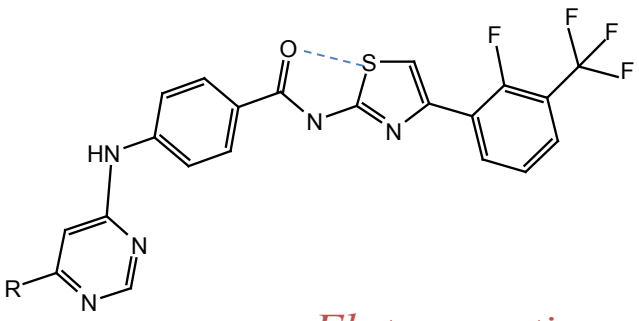
Molecule	logS0 (exp)	ΔHsubl(exp)	ΔGhydr(the)
ethane	-1.36	4.9	1.93
propane	-1.94	6.81	1.93
pentane	-3.18	10	2.25
hexane	-3.82	12.1	2.42
heptane	-4.53	13.8	2.6
octane	-5.24	16.3	2.78
nonane	-5.88	17.8	2.95
cyclopentane	-2.64	10.2	0.57
cycloheptane	-3.51	12.8	0.45
cyclohexane	-3.1	11.1	0.43
cyclooctane	-4.15	14	0.53
benzene	-1.64	10.8	-1.16
phenol	0	15.61	-6.81
biphenyl	-4.35	19.9	-1.66
naphthalene	-3.6	17.7	-1.53
toluene	-2.21	10.3	-1.12
2-naphthol	-2.28	21.5	-7.59
benzamid	-0.96	23.2	-9.93
indole	1.21	17.9	-6.63
p-nitrotoluene	-2.49	18.91	-4.31
ethylene	-0.4	4.37	2.22



$$\log S_0 = -0.417\,\Delta H_{sub} - 0.73\,\Delta G_{hydr} + 2.41$$

Abramov, Y.A. unpublished results. **2005**

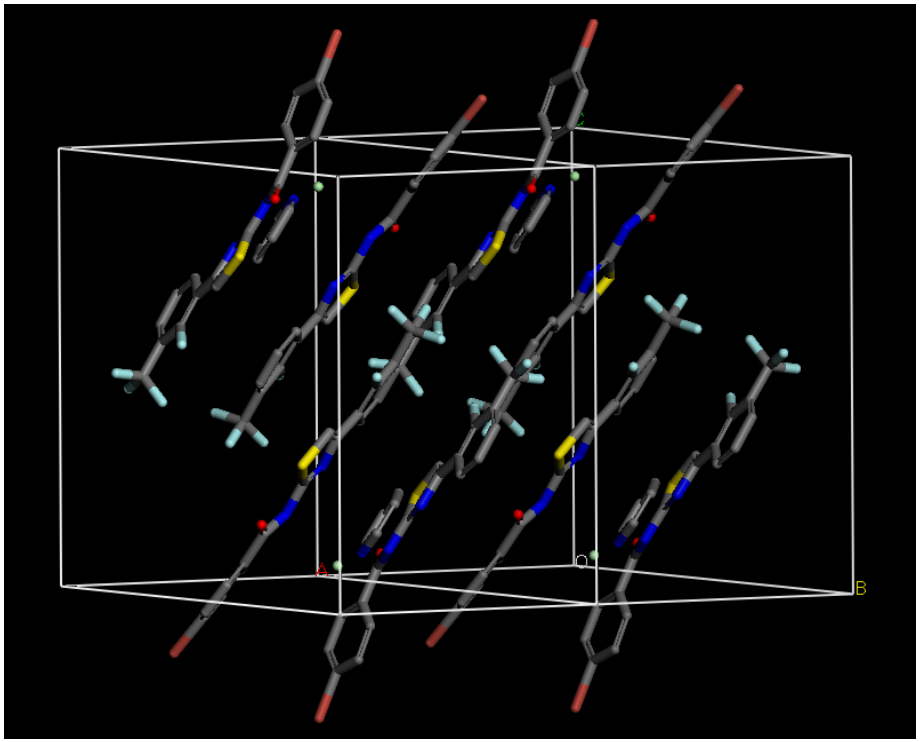
Case study: Thermodynamic cycle calculations to drive solubility improvement: Crystals with Strong π-stacking



Reiter, L.A. et al. BMCL, 2007, 17, 5447.
Reiter, L.A. et al. BMCL, 2008, 18, 3000.

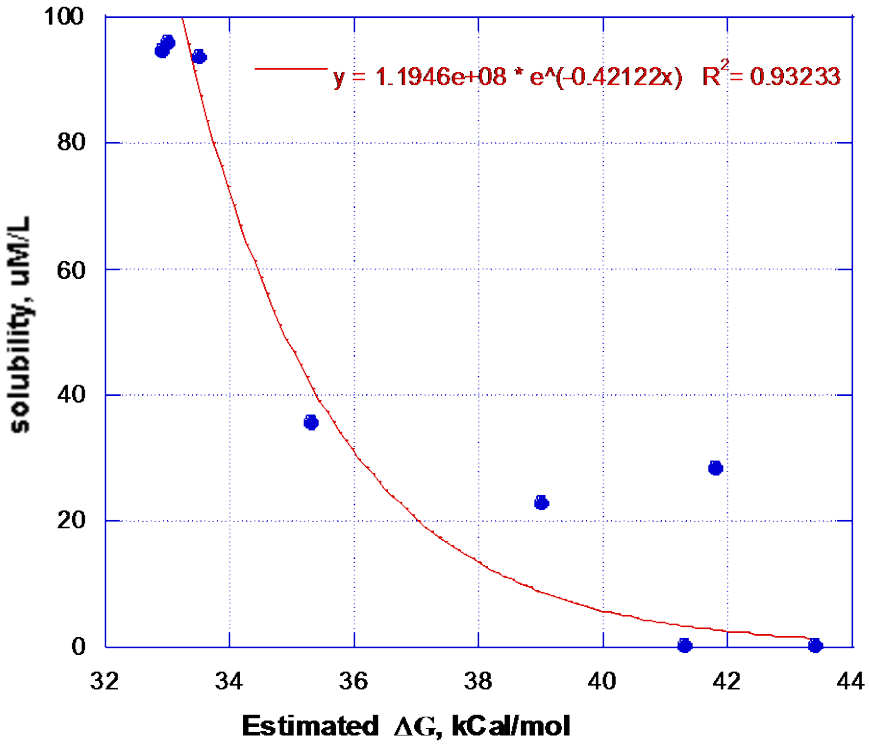
Lupyan, D.; Abramov, Y.A., Sherman, W. *JCAMD.***2012**,26,1195

Flat aromatic molecule displays a strong lattice packing



Solubility Modeling: Crystals with Strong π-stacking

Abramov, Y.A. unpublished results. **2005**



Crystal structure prediction was performed to estimate ΔG_{sub} for different molecule modifications.

Current work:

Docherty, R.; Pencheva, K.; Abramov, Y.A. *J Pharm. Pharm.* **2015**, *in press*

Conclusions

- An accurate QSPR model was built which allows identification of compounds susceptible to oxidative instability, and together with the QM model provides an opportunity to overcome this problem at early stage of drug discovery.

- It was demonstrated that the COSMO-RS G_{ex} property provides the most efficient way of virtual screening of hydration propensity of solid pharmaceutical compounds. It was also demonstrated that a virtual coformer screening based on the API coformer miscibility, as measured by the COSMO-RS H_{ex} property, may be efficiently used to guide the experimental selection of coformers to provide the highest RH stability.

- The selection of the commercial solid form is a key deliverable in the pharmaceutical industry. A focus was given to such methods as CSP and H-bonding propensity analyses.

- Analysis of the relative contributions of the ΔG_{sub} and ΔG_{hyd} into a poor solubility should be considered to drive solubility improvement.

Acknowledgment

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- Aurora Cruz-Cabeza
- Cheryl Doherty
- Bob Docherty
- Brian Samas